Electrochemical oxidation of isochromanones, isoquinolines and related structures

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Electrochemical Oxidation of Isochromanones, Isoquinolines and Related Structures

submitted by

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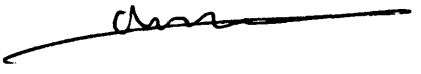

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Finally I wish to thank Mrs. V. Edwards for typing this thesis.

Summary

The work described in this thesis related to several inter-related topics: (a) the synthesis and electrochemical oxidation of N-aralkyl-1,2,3,4-tetrahydroisoquinolines and (b) similar studies with 3- and 4-aralkyl-1,2,3,4-tetrahydroisoquinolines.

In addition a major study of the mechanisms by which 4-benzylisochroman-3-ones undergo anodic coupling has been undertaken. Finally some preliminary steps *en route* to the synthesis of 4-benzyl-1,2,3,4-tetrahydroquinolines have been examined.

Contents

INTRODUCTION

(i) Organic Electro-oxidative Chemistry

The electrochemical oxidation of organic molecules is certainly not new; it has its origins in the middle of the last century when Kolbe[1] studied the syntheses of alkanes by the anodic oxidation of carboxylate anions:

$$2RCOO^- \xrightarrow{-2e^-} 2RCOO^{\bullet} \longrightarrow 2R^{\bullet} + 2CO_2$$

$$2R^{\bullet} \longrightarrow R\text{-}R$$

The Kolbe synthesis has received much attention from organic chemists[2] over the years, mainly due to the wide variety of acids that undergo decarboxylation under simple experimental conditions, but this is an isolated example. However, in the early nineteen hundreds, small scale industrial electrochemical processes were used for the preparation of intermediates for the dyestuffs industry, such as benzidine and anthraquinone[3,4], but from then until the middle of the century there was an apparent lack of interest in anodic oxidation. The main reason for this has been the difficulties experienced in interpreting complex electrode processes. The development of cyclic voltammetry has largely overcome this particular problem by aiding the elucidation of reaction mechanisms occurring at the electrode. In recent years electrochemical reactions have been increasingly considered by organic chemists as alternatives to the use of

conventional chemical reagents, since most chemical reactions involve addition or removal of electrons and reagents are becoming increasingly more expensive.

Radical cations formed by the removal of electrons from organic molecules at the anode are generally highly reactive and combine rapidly in secondary chemical processes to form more stable derivatives. The electrode process is therefore essentially irreversible and classical theories (e.g. the application of the Nernst equation based on electrode process reversibility) cannot successfully be applied to anodic reactions.

Organic electrochemistry is now a very broad subject and only a limited aspect of the topic is considered in this thesis, where the main theme will be an analysis of the anodic oxidation of selected aromatic and heteroaromatic substrates leading to intramolecular coupling reactions.

(ii) Some Basic Electrochemical Laws

In 1834, Faraday[5] described the relationship between the quantity of electrical charge consumed in an electrolysis and the amount of material used. His conclusions are:

(i) The amount of material transformed is proportional to the quantity of charge passed (Q)

(ii) The mass of the various materials transformed (W) are proportional to their respective molecular weights (M).

This leads to the equation:

$$W = \frac{MQ}{96,495n}$$

Where the number 96,495 is the "Faraday" which is the number of coulombs necessary to transfer one molecular equivalent of substrate in a one electron reaction. The letter "n" represents the number of electrons transferred per molecule of substrate.

The consumption of one Faraday of charge per molecular equivalent rarely results in the formation of one equivalent of product, and losses in energy due to convected heat and electrochemical side reactions, possibly involving the electrolyte, must be taken into account.

(iii) Cyclic Voltammetry

Classical polarography, first introduced by Heyrovsky[6] in the 1920's has largely been superseded by other electroanalytical techniques. Further, the introduction of new types of microelectrodes is making the study of electrode kinetics considerably more easy. Cyclic voltammetry is able to provide approximate data on the potentials at which to conduct preparative electrolyses and also enables an analysis of the probable events occurring after the initial ionisation step to be predicted.

An expression which determines the maximum diffusion limiting current of a polarographic peak has been derived by Ilkovic[7], but this is of little relevance to this discussion. Of much greater

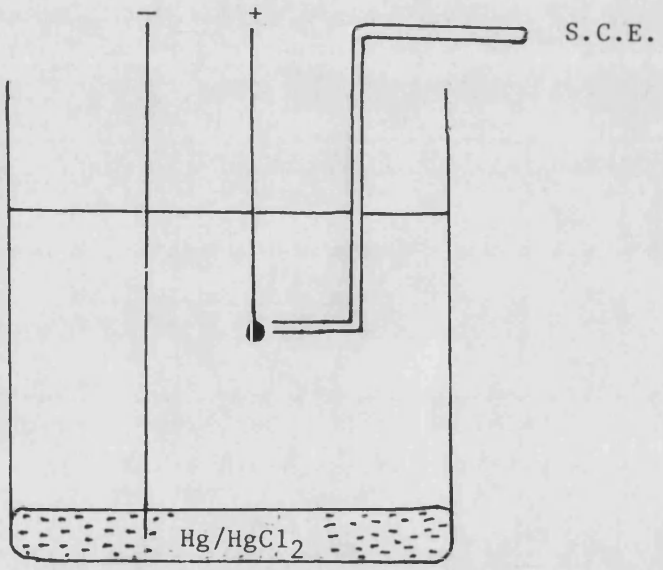
importance is a description of linear scan voltammetry and the closely related cyclic voltammetry. There are two main differences between conventional polarography and voltammetry. These are:

(i) the time scale on which a voltage sweep is made, and

(ii) the type of working electrode that may be used.

The electrodes used in voltammetry can be the same as those employed in preparative electrolyses and platinum bead, or wire microelectrodes are the most common. They are often used in conjunction with a simple one-compartment cell (figure 1)

Figure 1.

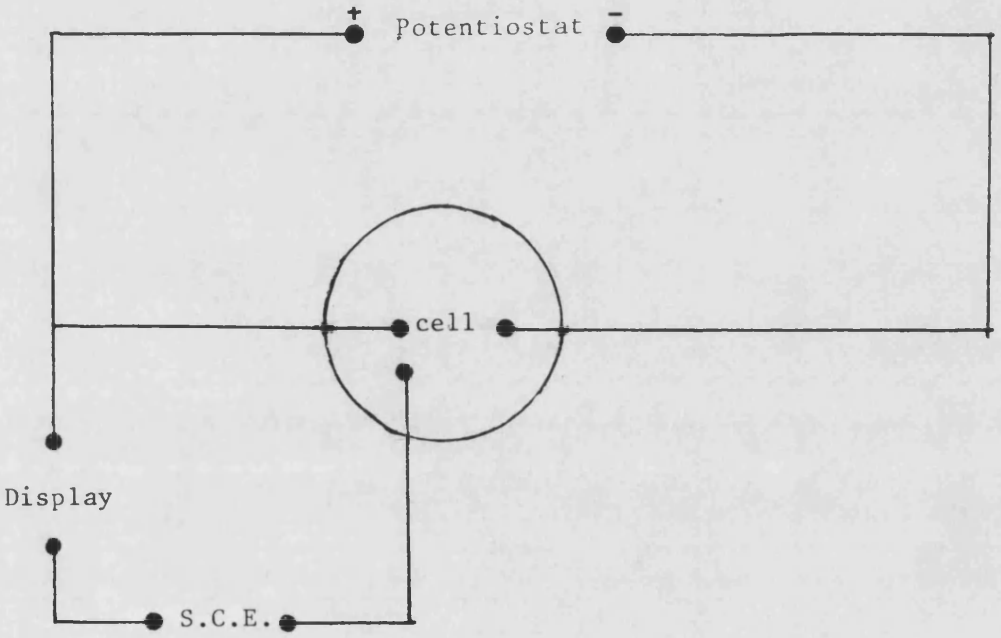


S.C.E. standard calomel electrode

This cell actually comprises three electrodes. These are the working electrode itself, a suitable counter electrode, and a reference electrode, Ag/AgCl, or calomel. Anhydrous conditions are necessary, and an inert gas atmosphere is preferable.

In cyclic voltammetry the electrode potential is linearly swept, whilst the current through the working electrode is constantly monitored (figure 2).

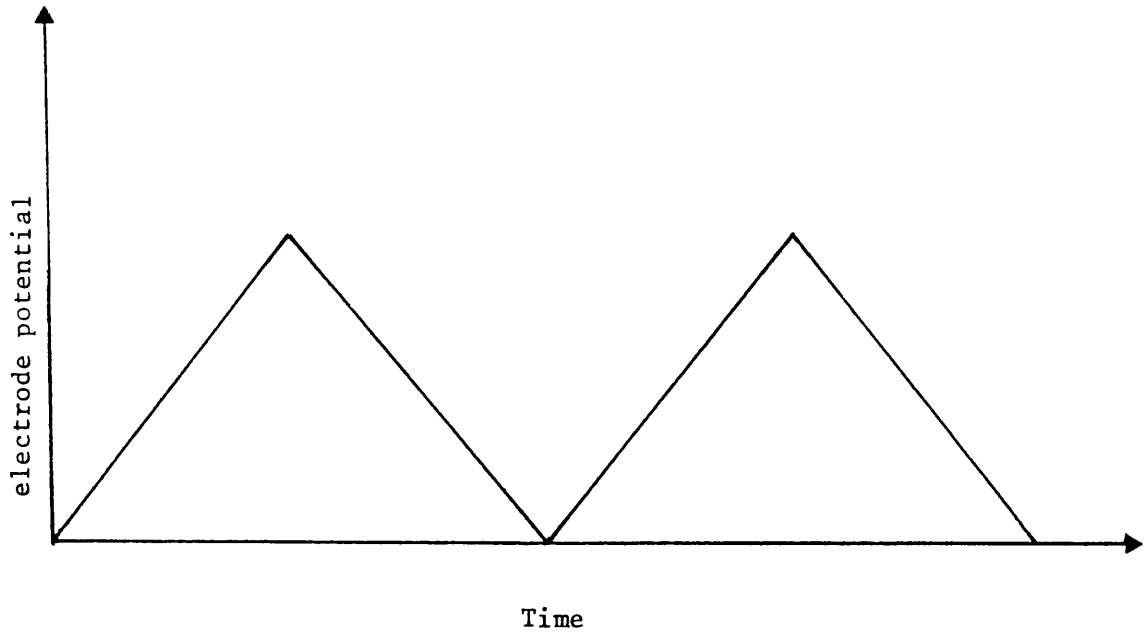
Figure 2.



Usually a triangular, or sawtooth, waveform is applied to the working electrode and this is represented as the "X" ordinate on an oscilloscope or a "X-Y" plotter. (figure 3).

The current change is measured as the change in potential difference across a "counting" register and is displayed as the "Y" ordinate on the recording device.

Figure 3.



Generally the technique is used in two distinct modes of operation:

(i) A single sweep operation, where sufficient time is allowed to elapse between scans for the initial concentration of the substrate to be regained in the diffusion layer of the electrode, prior to a subsequent sweep.

(ii) Multisweep techniques, where a continuous sawtooth waveform is applied to the electrode. Due to the secondary chemical processes which normally occur in organic electrode reactions, the first and second sweeps are often quite different to later results since steady state conditions normally are reached after five to ten cycles.

Some examples will ilustrate the value of cyclic voltammetry

to the organic chemist.

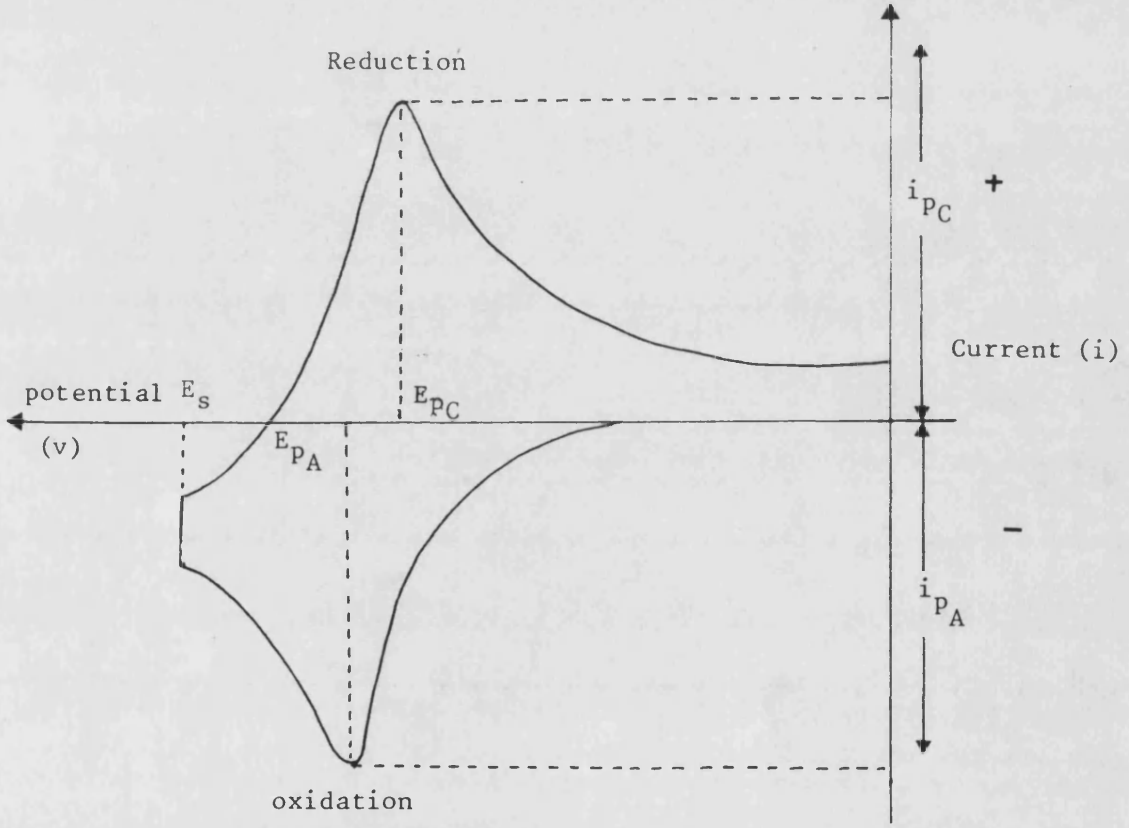
(a) The first case to be considered is that of a reversible one electron process. Here as the electrode potential increases in the cell current begins to flow and the electroactive substrate (S) is oxidized.

$$\overset{\cdot\cdot}{S} \rightleftharpoons S^{\cdot +} + e$$

The current then rises rapidly until all the electroactive material around the electrode is consumed and the supply of substrate by diffusion from the bulk phase is exceeded. At this point the current falls, giving rise to a point of inflexion in the voltammogram (E_{p_A}, figure 4). At this time the concentration of substrate decreases to zero. The maximum current (i_{p_A}) is thus proportional to the peak height. It is also true that the peak potential (E_p) of a reversible oxidation is independent of scan speed[8], but this is not true of an irreversible process[9], this can be a useful criterion in determining reversibility. At a predetermined value (E_s, the switching potential) the voltage sweep is reversed and current flows in the opposite direction. At this point the electrode is surrounded by oxidised species which are then reduced at the appropriate potential (E_{p_C}) giving rise to a reduction peak.

For a truly reversible reaction the ratio of peak currents (i_{p_C} / i_{p_A}) will be unity.

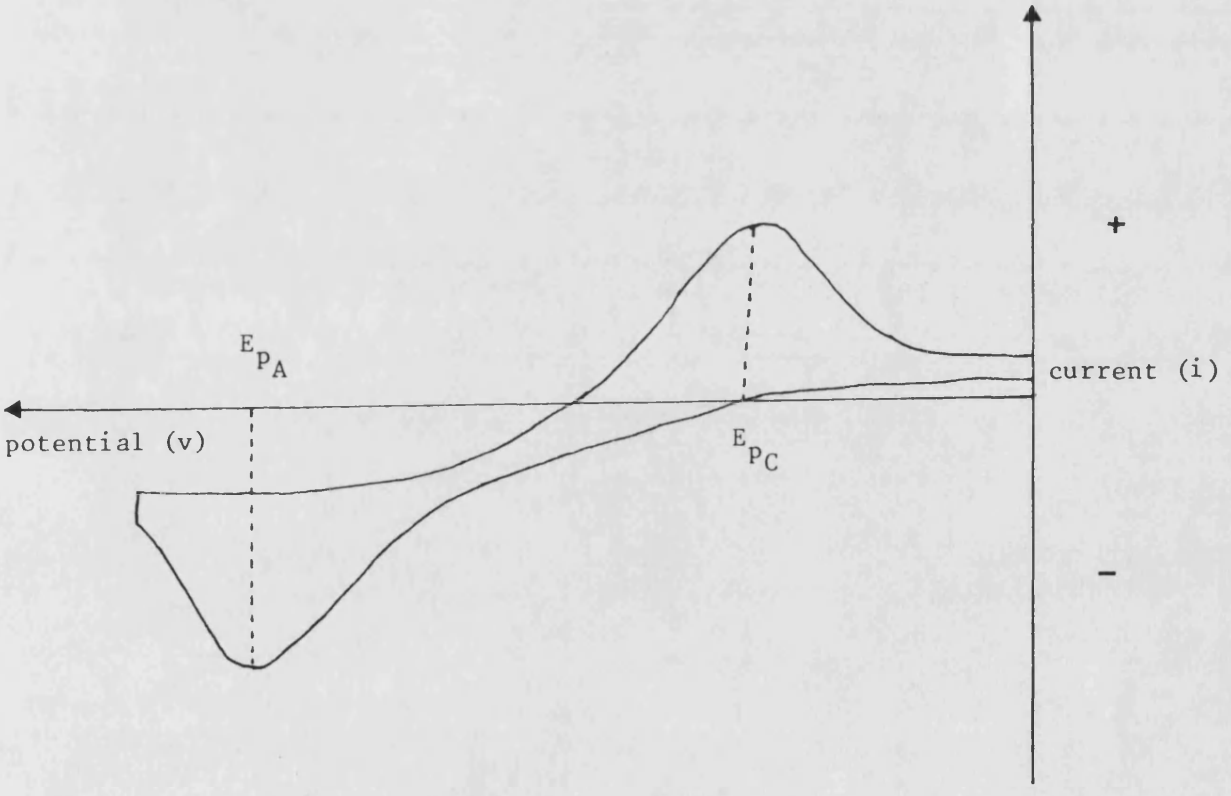
Figure 4.


Reduction
i_{P_C}
+
Current (i)
potential E_s
(v)
E_{P_C}
E_{P_A}
i_{P_A}
−
oxidation

(b) A second general example is that of a slow charge transfer irreversible oxidation, without an accompanying chemical reaction (figure 5). Generally speaking in this case, peaks will be broader at higher scan speeds and oxidative peaks will become progressively more anodic on increasing the scan speed. Reductive peaks will be displaced equally, but in a cathodic direction. Clearly the distinction made between reversible and irreversible processes is an artificial one and is only based on the rate of charge transfer processes, which can be affected by both background electrolyte and electrode material.

Figure 5.

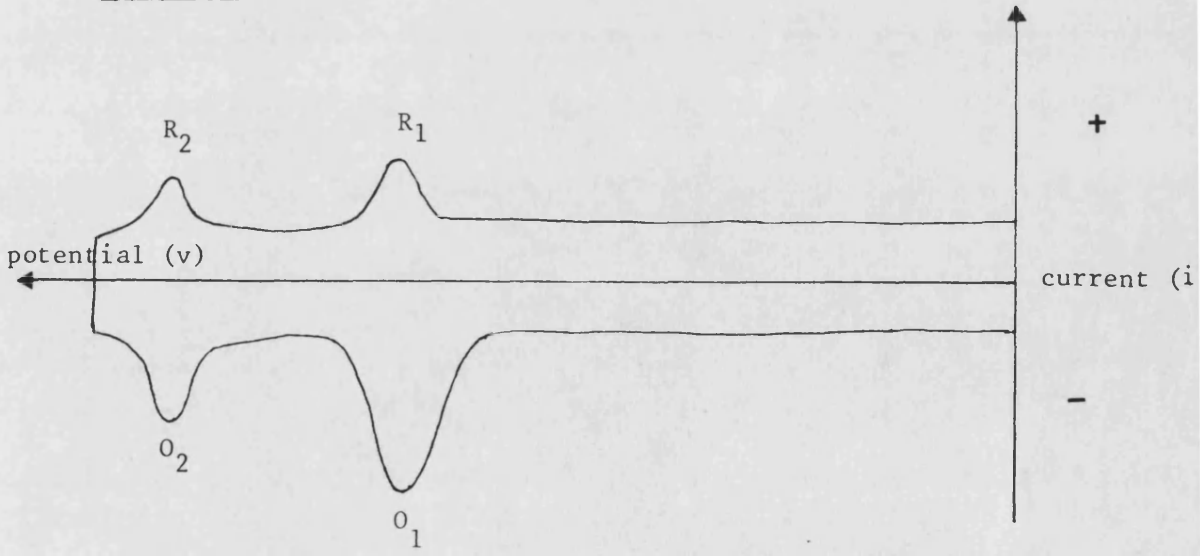
$E_{P_A} - E_{P_C} \propto \frac{1}{v^{\frac{1}{2}}}$



As a corollary, Nicholson[10] has described methods for evaluating rate constants of electron transfers from peak separation at varying scan speeds.

(c) In the third case of a reversible process this time with an associated chemical reaction (figure 6) the compound is oxidised at a potential O_1 to produce an oxidised species which is sufficiently reactive to form a product which is then oxidised at a higher potential O_2. If complete conversion of the substrate has not been affected by the time the voltage sweep has recycled then the residual oxidised species will be reduced and a reductive peak R_1 will be observed. R_1 will not be seen if the oxidised species undergoes a fast chemical reaction at a rate comparable to the time scale of the sweep. R_1 will always be less intense than O_1 and on the second and subsequent cycles O_1 will be reduced in intensity. A second reduction peak R_2 may be observed due to the reduction of the species formed by the second oxidation O_2.

Figure 6.



We have made two assumptions in proposing this last case. Firstly that the chemical product has a higher oxidation potential than the starting substrate, and that it forms a stable redox couple (O_2-R_2). In practice, however, the chemical product is oxidised close to, or below, the potential of starting material[11] and on oxidation, undergoes further chemical reactions. Over-oxidation is one of the main factors responsible for low yields in some coupling reactions.[12]

Quantitative assessment of the number of electrons involved in a mechanistic sequence can be made by integrating the voltammogram electronically and comparing the integral height with that of an equimolar solution of 1,4-dimethoxybenzene, known to be oxidised in a one electron process at a potential of +1.34 volts.

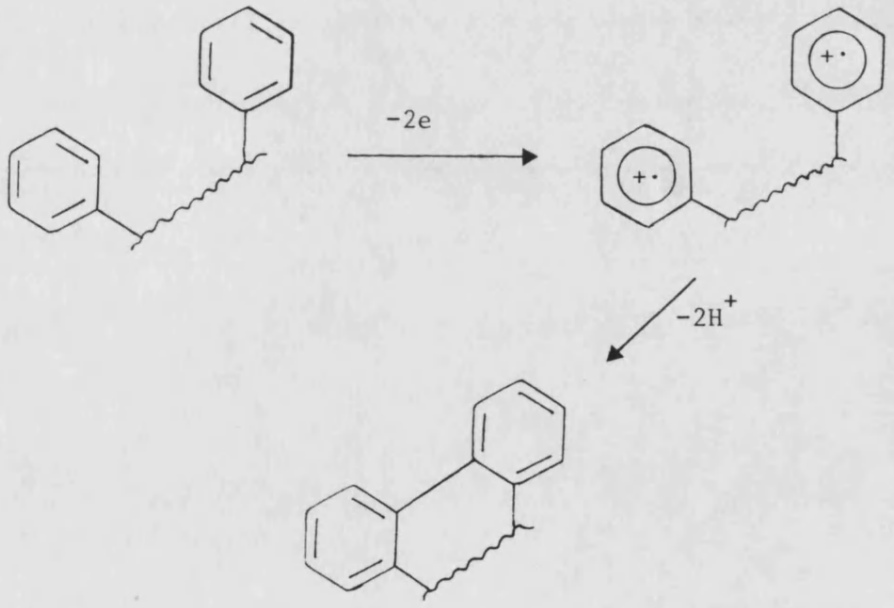
Conclusions

In approaching the study of a electrochemical problem, such as that presented by an electro-synthesis, the results of a simple cyclovoltammetric scan of the substrate is invaluable. From it may be judged, not only the potential required, but events after the initial electrode reaction. Indeed it is possible to ascertain if the electrolysis is likely to succeed, for should the second sweep reveal an anodic (or cathodic) peak at lower potential than that exhibited by the substrate then it is obvious that the product will undergo further oxidation, or reduction, and it will not be an easy task to isolate pure compounds.

(iv) The Mechanism of Aryl-Aryl Electrochemical Oxidative Coupling Reactions

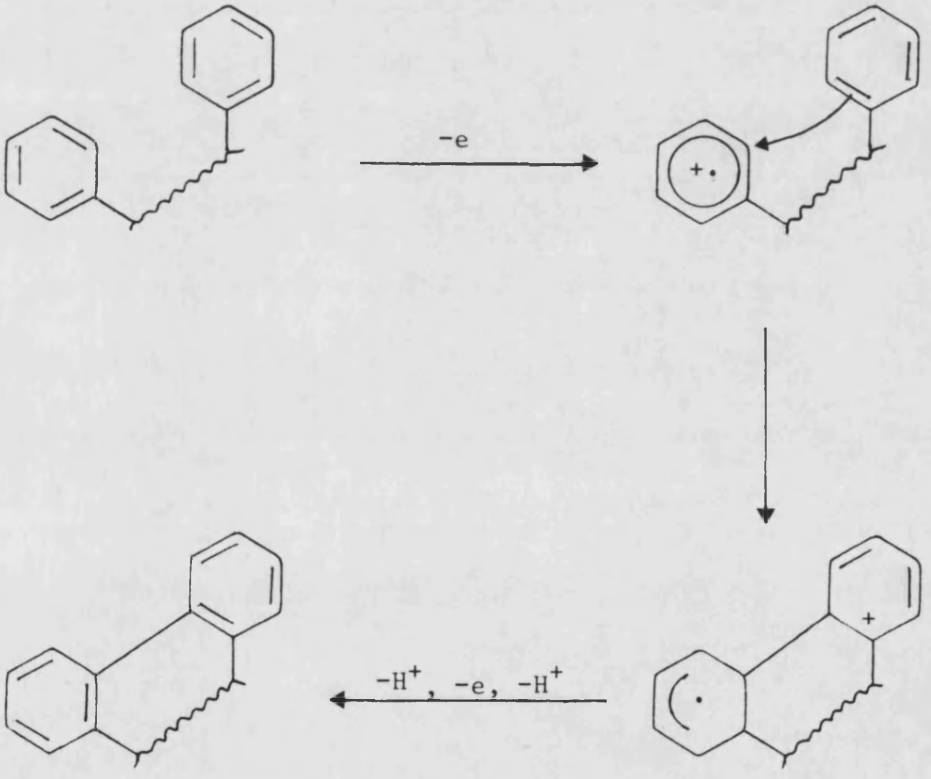
The exact sequence of events in electrooxidative coupling reactions leading to para-para coupled products has been the point of some conjecture. Three different mechanisms of coupling have been proposed[12,13,14], Parker[14] has suggested the "eec" reaction (scheme-1). This involves the loss of two electrons in sequence, one from each of the aryl rings, followed by a chemical reaction. The approach of two positively charged aryl nuclei seems unlikely at first sight, but this type of reaction mechanism is often assumed and quoted commonly in the literature.[12]

Scheme 1.



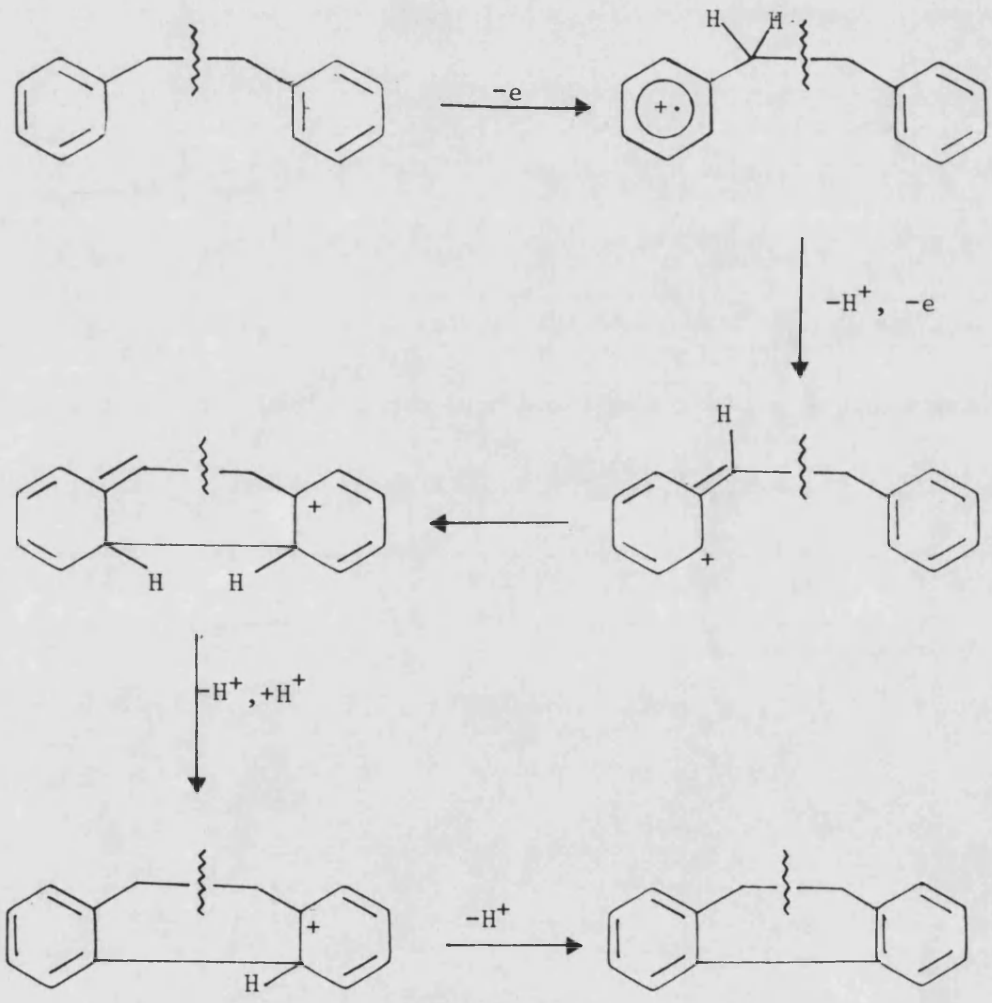
The alternative "ece" reaction (scheme-2) has been advanced by Nyberg[13]. One of the aryl rings is oxidised and coupling then occurs with the π-system of non-ionised nucleus. This is then followed by loss of a second electron and a proton; the overall result is, of course, the same, as that of the "eec" mechanism, but it does avoid the problem of repulsive interaction of similarly charged species noted above.

Scheme 2.

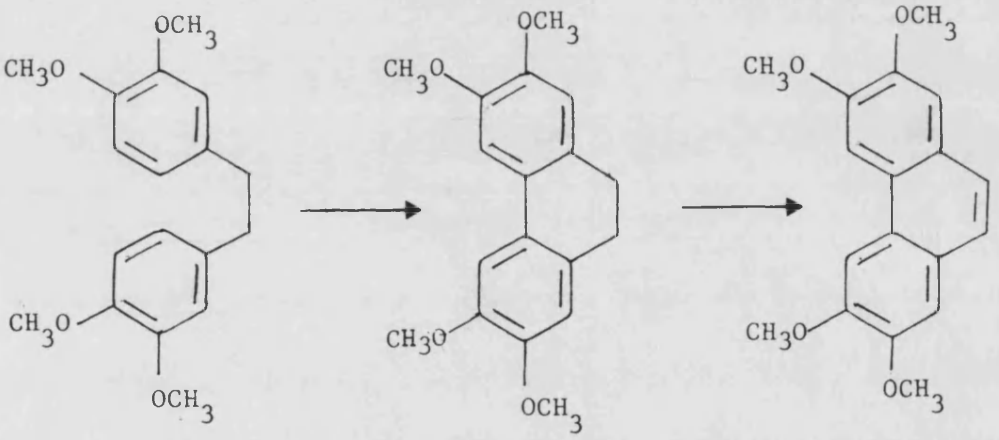


The third route, for special cases, has been proposed by Sainsbury, although never published, and involves stabilisation of the intermediate, formed after electron loss as a benzylic cation (scheme-3). There are a number of reasons for this hypothesis, but the most obvious one is the fact that many benzylic substrates do undergo anodic deprotonation at the position α- to the arene ring.

Scheme 3.



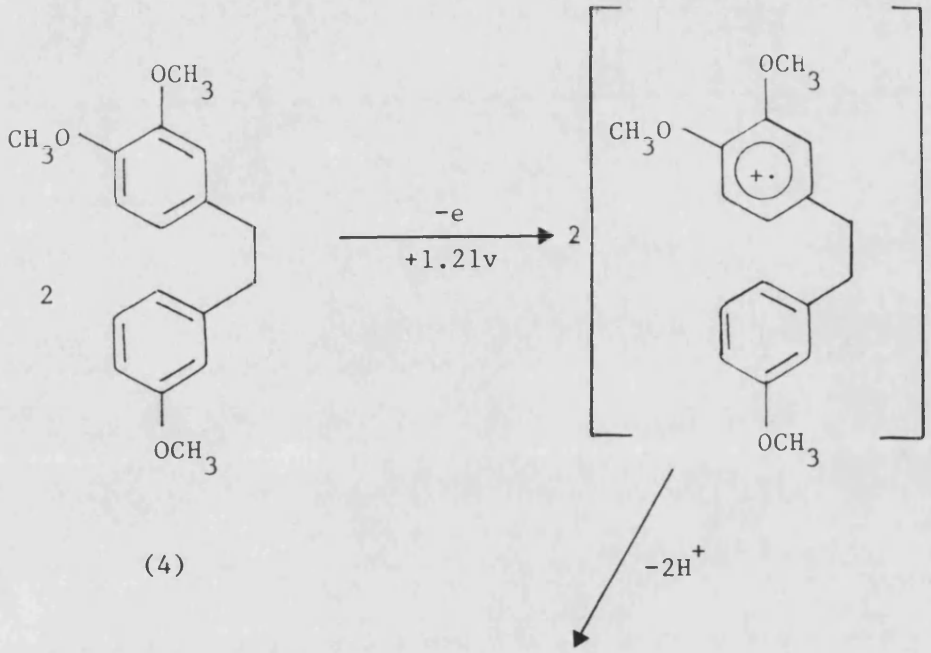
A understanding of the true nature of the coupling process is important for it may then be possible to rationalise many anomalous results which are quoted in the literature. In this laboratory, and elsewhere, a great deal of work has been carried out on the electrochemical oxidation of diarylalkanes as a prelude to studies with more complex substrates. Anodic oxidation of 3,3',4,4'-tetramethoxybibenzyl (1), for example, has given the dihydrophenanthrene (2) which is further oxidised to the phenanthrene (3).[15]



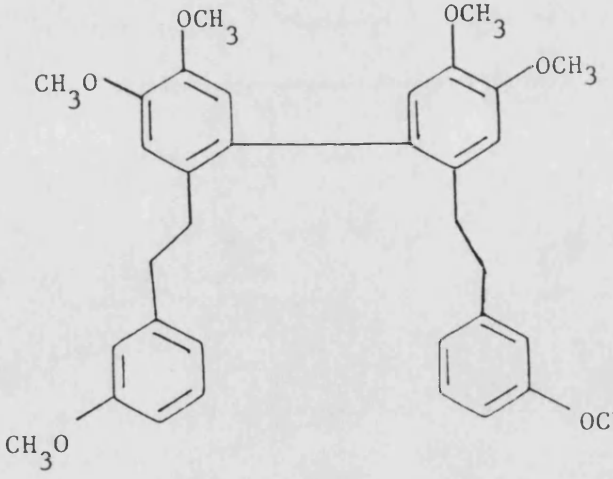
(1) (2) (3)

One piece of evidence for the "eec" mechanism comes from this work for oxidation[12] of the unsymmetrical 3,3',4-trimethoxybibenzyl (4) at +1.21 volts gives rise to the dehydrodimer (5), by initial oxidation of the dimethoxy ring. This affords a radical cation which then interacts with itself, or more substrate, to yield (5). If a higher potential is used the solution concentration is lowered to offset "dimerisation"

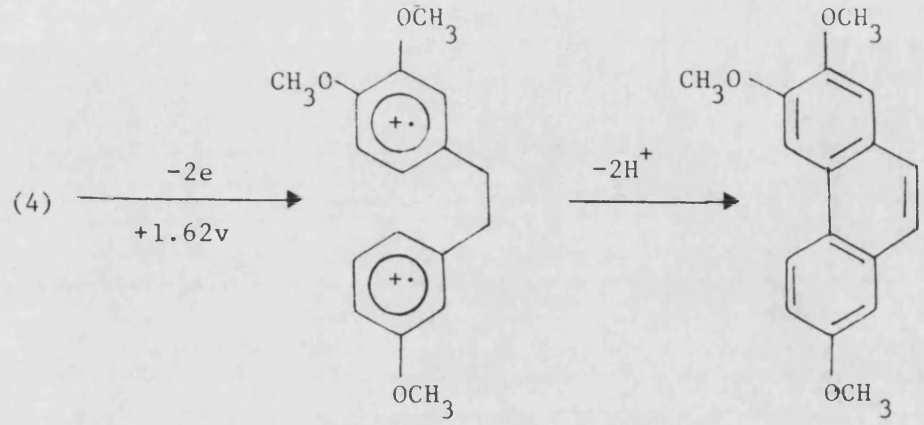
the phenanthrene (7) is produced, it is said, by participation of the dication diradical (6).



(4)

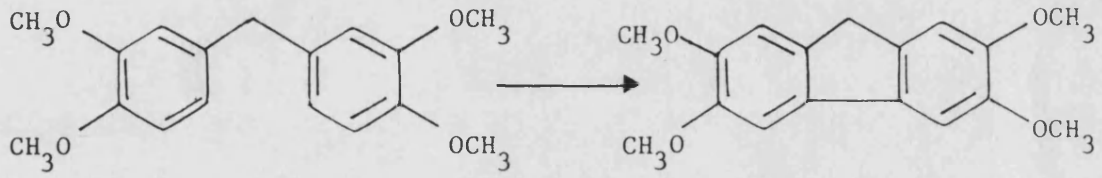


(5)

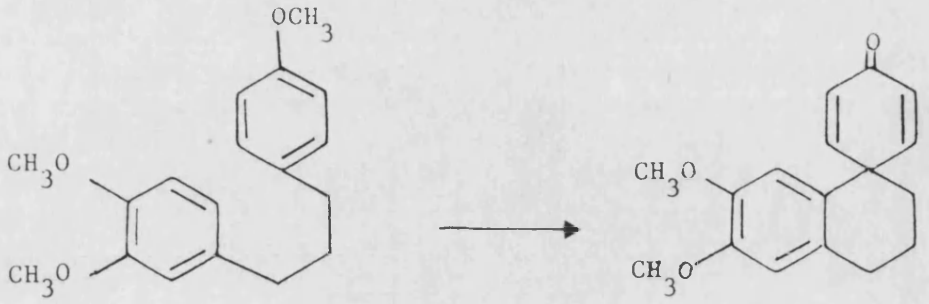


(6) (7)

Some further early examples of aryl-aryl couplings are that of 3,3',4,4'-tetramethoxydiphenylmethane (8) which on anodic oxidation gives the bridged biphenyl (9)[16] and oxidation of the diarylpropane (10) known to give the spirodienone (11)[17].



(8) (9)



(10) (11)

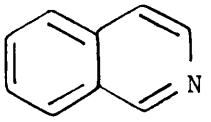
These results were "inspirational" and encouraged others to examine more complex substrates, particularly those likely to give rise to pharmaceutically useful structures. Some of these studies will be considered later in this introduction.

(v) The Synthesis of Isoquinolines and 3,4-Dihydroisoquinolines

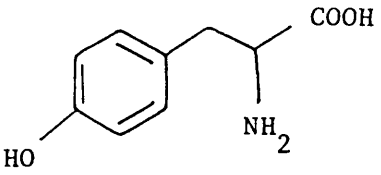
Many of the substrates studied in this work are isoquinolines and thus it is appropriate to consider the ways that such compounds are synthesised.

Isoquinoline (12) was first reported in 1885[18] when it was extracted from coal tar. Indeed many types of isoquinolines have been isolated subsequently from natural sources: principally coal tar, petroleum oils, and plants. By far the largest number of

isoquinoline derivatives have been obtained from plants which form isoquinoline alkaloids. These are biosynthesised from tyrosine (13) and related aromatic amino acids via the shikimic acid pathway.



(12)



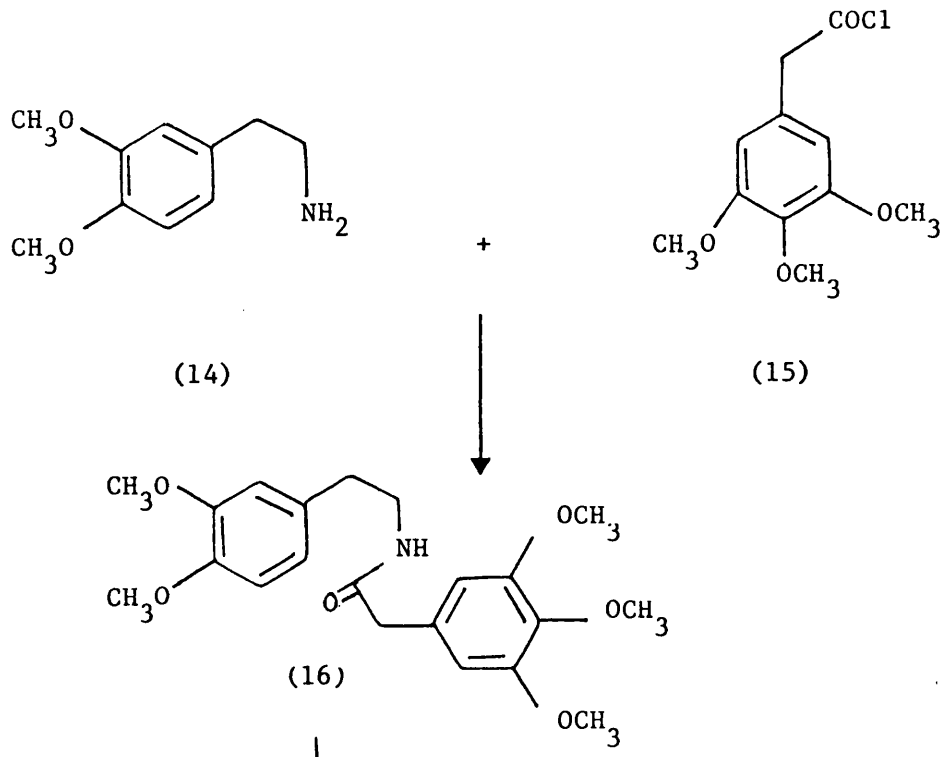
(13)

The frequent occurrence of the isoquinoline nucleus in Nature and in some physiologically active compounds has led to great interest in the construction of isoquinoline derivatives. The classical methods of synthesis comprise the familiar Bischler-Napieralski, Pictet-Spengler, and Pomeranz-Fritsch reactions. In recent years many modifications of these classical routes have been published in addition to some new approaches.

1. The Bischler-Napieralski reaction

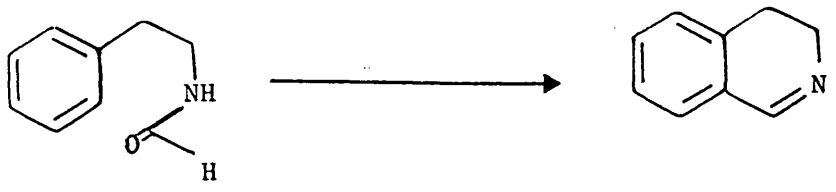
The original Bischler-Napieralski method which yields a 3,4-dihydroisoquinoline as the initial product[19] depends upon the ring closure of a β-arylethylamide with a mixture of phosphoryl chloride and phosphorus(V) oxide. The product may

then be oxidised to the fully aromatic isoquinoline, or reduced to the 1,2,3,4-tetrahydroisoquinoline. For example, the β-arylamine (14) when treated with acid chloride (15) forms the β-arylamide (16) which on treatment with phosphoryl chloride yields the 3,4-dihydroisoquinoline (17).[20]



(17)

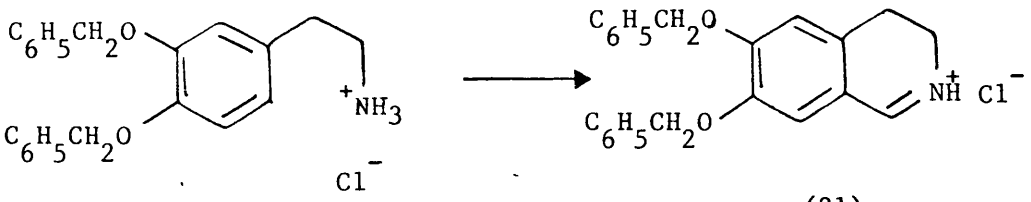
Many reagent combinations other than phosphoryl chloride and phosphorus(V) oxide have been used, for example, phosphoryl chloride[21,22] has been employed alone, and similarly useful is phosphorus(V) oxide in pyridine[23]. More recently polyphosphoric acid has been recommended and this is especially useful for the cyclisation of formamides[24], as in the case of the simple deactivated amide (18) which was cyclised to give 3,4-dihydro-isoquinoline (19) in very high yield.



(18) (19)

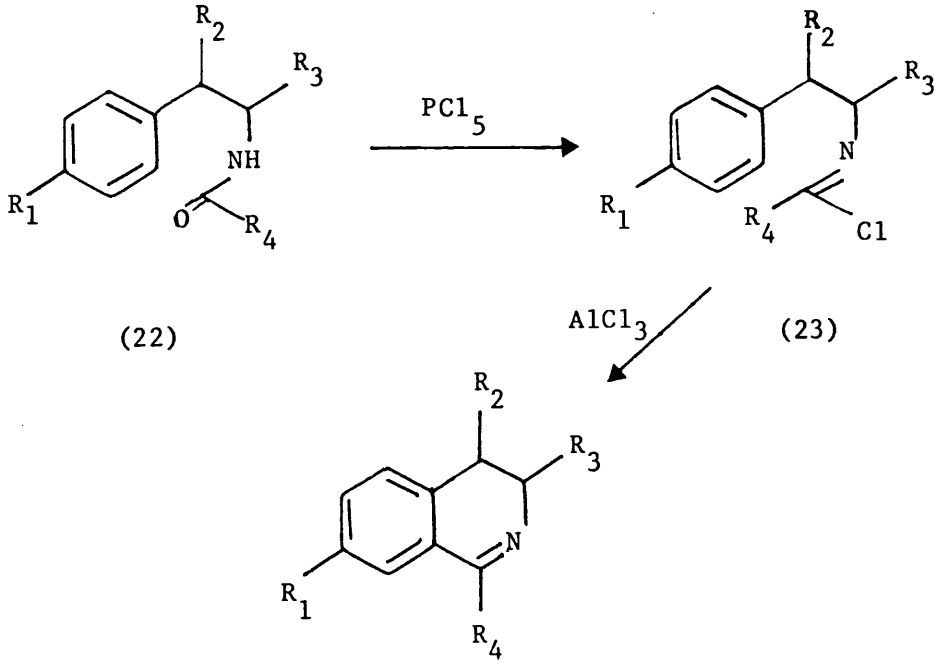
Polyphosphoric ester (PPE) is another relatively modern reagent and its use requires less severe conditions than many of the older cyclisation agents.

Several modifications have been made to the synthesis such as that introduced by Kador[25] which is especially useful for the preparation of 1-unsubstituted isoquinolines. In this the hydrochloride salt of the amine (20) is treated with trichloroacetaldehyde and phosphoryl chloride to form the 3,4-dihydroisoquinolinium salt (21).



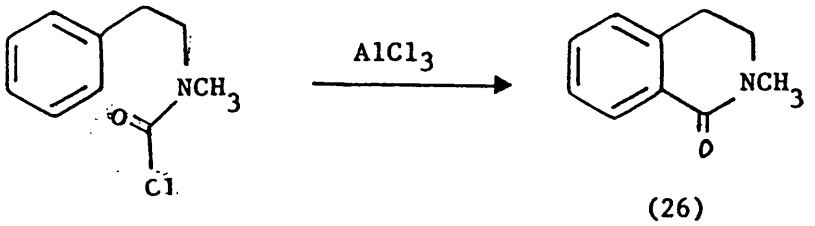
(20) (21)

Hey[26] reported a method whereby, if a normal Bischler-Napieralski reaction fails, the amide (22) can be converted with phosphorus pentachloride to an imidoyl chloride (23), which is then cyclised, using aluminium chloride, to the dihydroisoquinoline (24).



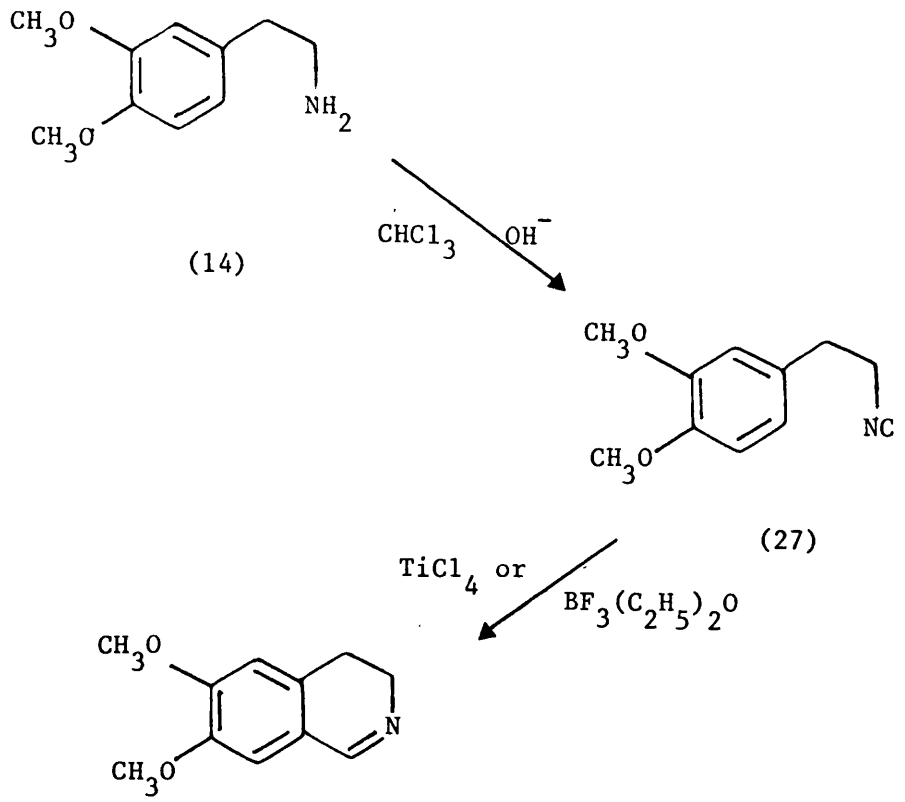
(22) (23) (24)

Aluminium chloride has also been used to convert methyl-β-phenylethylaminoacetyl chloride (25) into the tetrahydroisoquinoline (26)[27,28], but this approach is limited to those substrates that are free from alkoxyl substituents since the Lewis acid may cause O-dealkylation to occur as a side reaction.



(25) (26)

Yet another interesting varient of the Bischler-Napieralski reaction has been reported by Ban[29], in which the amine (14) is treated with dichlorocarbene to form the isocyanide (27) and this is then cyclised using either titanium tetrachloride or boron trifluoride etherate to the dihydroisoquinoline (28).



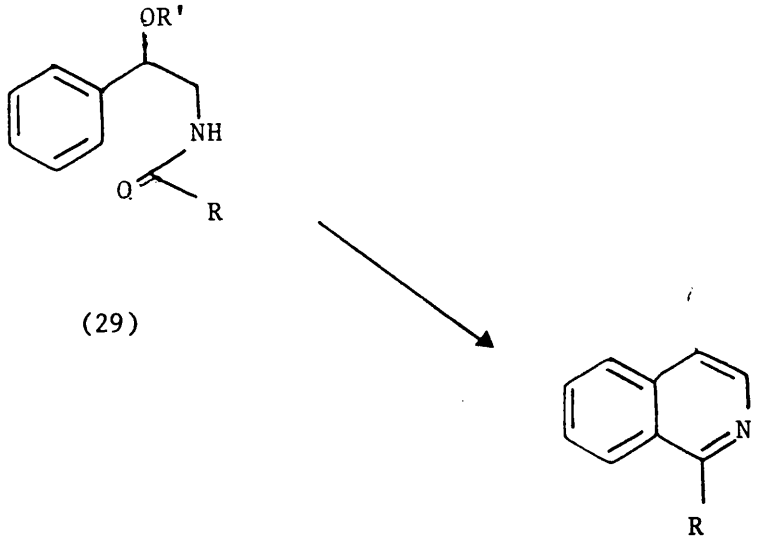
(14)

(27)

(28)

2. The Pictet-Gams reaction [22]

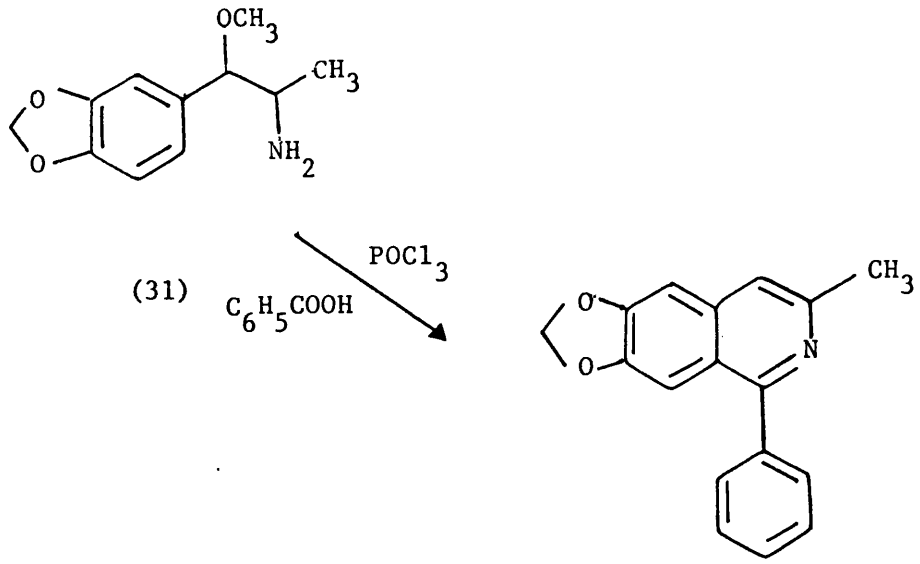
This is a modification of the Bischler-Napieralski reaction which leads directly to the formation of the fully aromatic isoquinoline (30) by starting with a β-hydroxy- or β-methoxy-substituted amide (29). Methods used to prepare appropriate amides (29) have been reviewed[30,31,32] and need not be discussed here.



(29) (30)

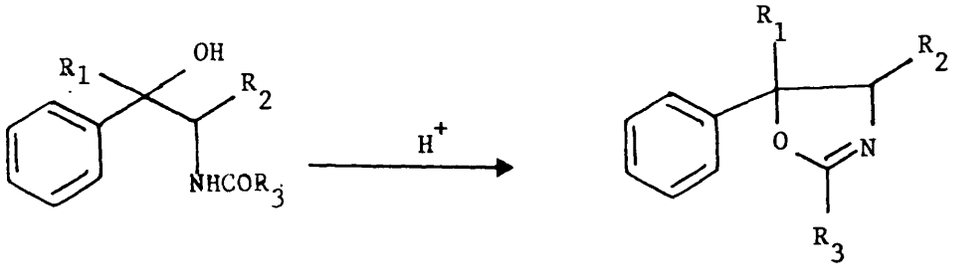
R' = (H, OCH_3)

In fact the isolation of the β-arylethylamide is not always necessary as is demonstrated in the case of the amine (31) which is converted directly into isoquinoline (32),[33] by heating with a mixture of benzoic acid and phosphoryl chloride.



(31) (32)

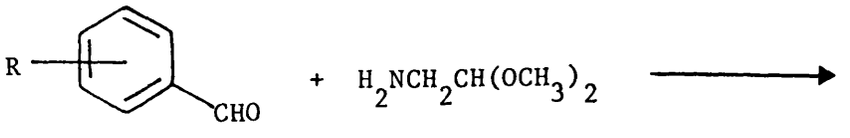
One adverse feature of the Pictet-Gams synthesis, however, is the production of oxazolines (34) through cyclisation of the amide (33) oxygen atom with the α-substituent of the side chain:



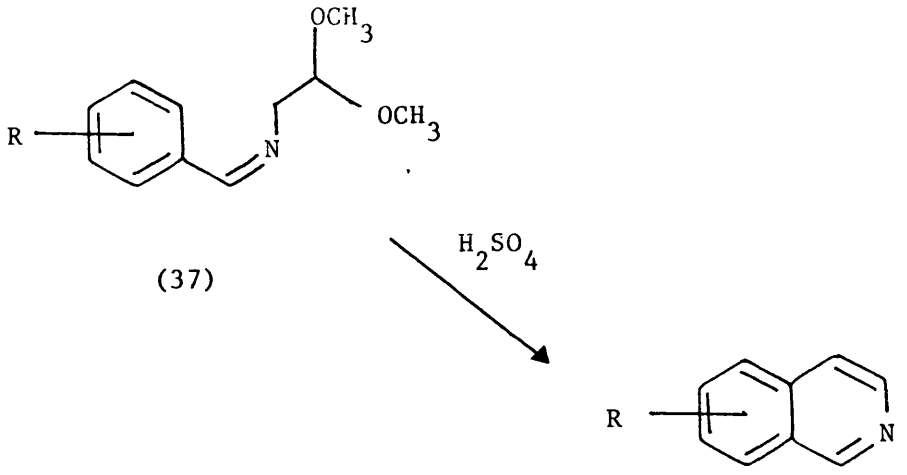
(33) (34)

3. The Pomeranz- Fritsch reaction [34,35]

The Pomeranz-Fritsch reaction is carried out in two stages. First of all an aromatic aldehyde (35) is condensed with aminoacetaldehyde dimethylacetal (36) to form a Schiff base, or anil (37). The second stage requires the acid-catalysed cyclisation of the anil to an isoquinoline (38).



(35) (36)

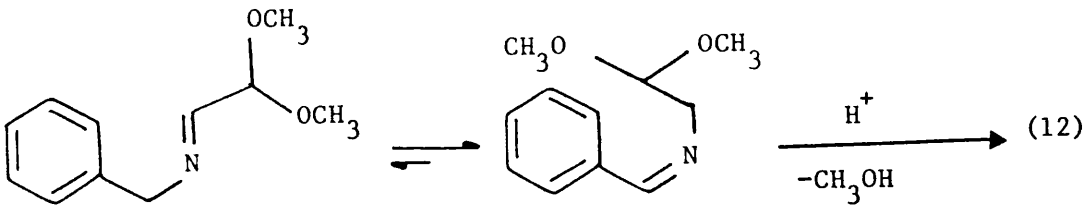


(37)

(38)

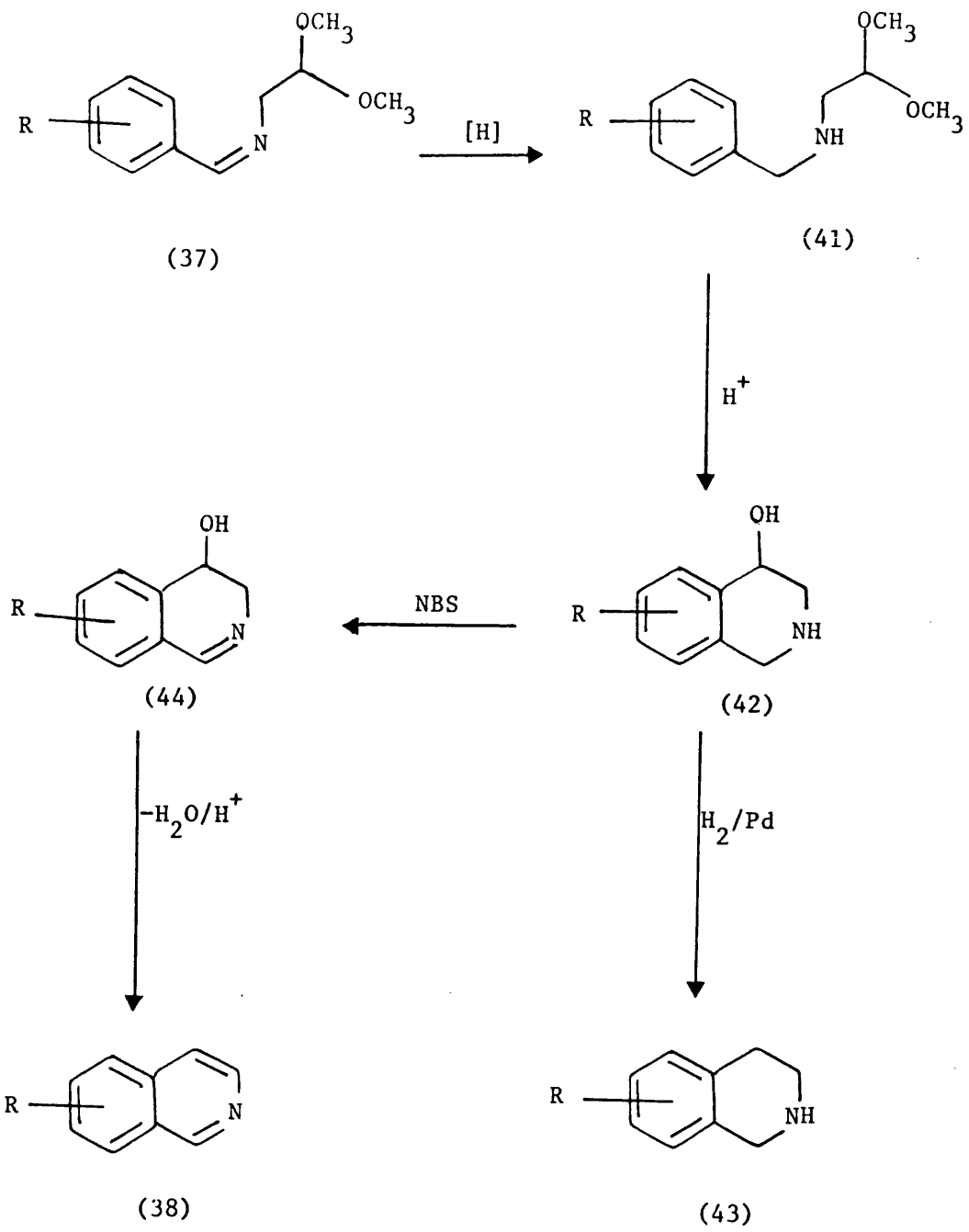
The ease of cyclisation depends on the susceptibility of the aromatic ring to electrophilic attack, so that if the ring is activated by electron donating substituents, the cyclisation occurs under mild conditions, whereas unsubstituted or deactivated substrates require much higher temperatures and more acidic conditions. Again there are a number of modifications of the Pomeranz-Fritsch reaction thus Schlitter and Muller[36] condensed benzylamine (39) with glyoxal semiacetal to give the Schiff's base (40) which may be cyclised with sulphuric acid to isoquinoline itself. Although this modification looks promising it has not been used much, probably because arene aldehydes are more easily available than the corresponding benzylamines.

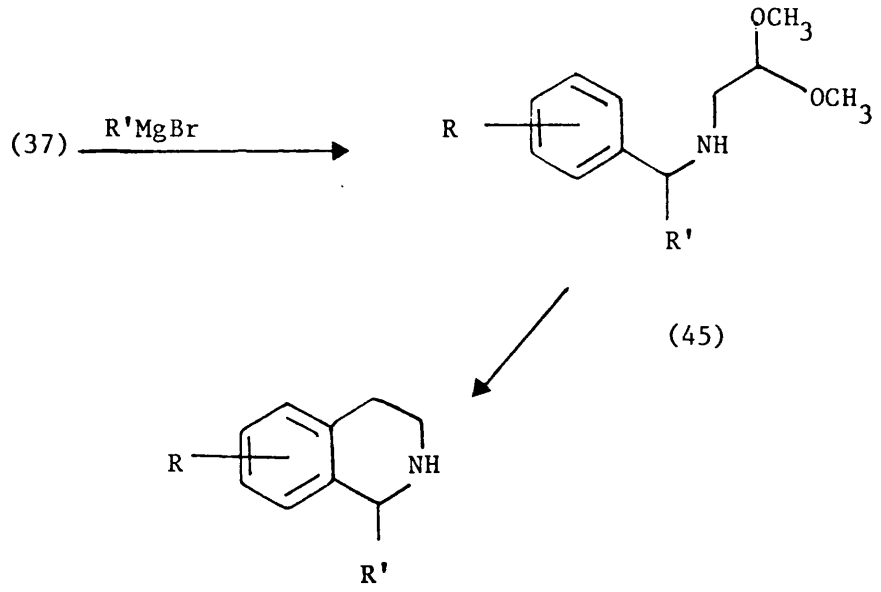
(39)



(40) (12)

A more useful technique has been introduced by Bobbitt[37,38] who has modified the Pomeranz-Fritsch reaction by catalytically reducing the Schiff's base e.g. (37) to the corresponding amine (41). This is then treated with 6M hydrochloric acid to afford a 4-hydroxy-1,2,3,4-tetrahydroisoquinoline (42)[39], which may then be hydrogenated to yield 1,2,3,4-tetrahydroisoquinoline (43) or oxidised with N-bromosuccinimide (NBS), and the product 4-hydroxy-3,4-dihydroisoquinoline (44) to give the fully aromatic isoquinoline (38). 1-Substituted isoquinolines may be prepared by a similar route whereby the Schiff's base (37) is treated with one equivalent of a Grignard reagent to form the resulting benzylamine (45) which may be then cyclised to the 1-alkyl or 1-aryl-1,2,3,4-tetrahydroisoquinoline (46) by treatment with acid.[40a]

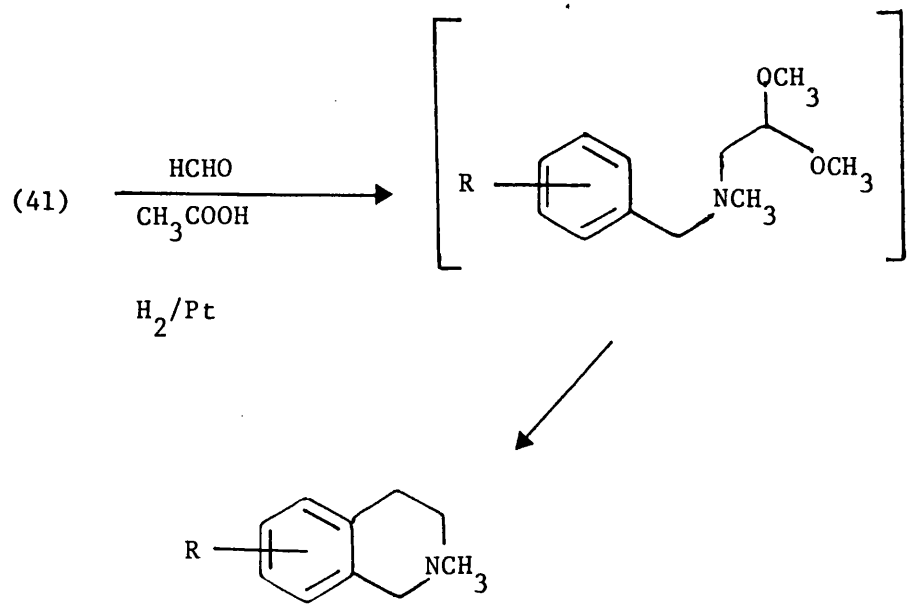

OCH3
OCH3
R
N
[H]
OCH3
OCH3
R
NH
(37)
(41)
H+
OH
OH
R
N
NBS
R
NH
(44)
(42)
-H2O/H+
H2/Pd
R
N
R
NH
(38)
(43)



R = alkyl, aryl

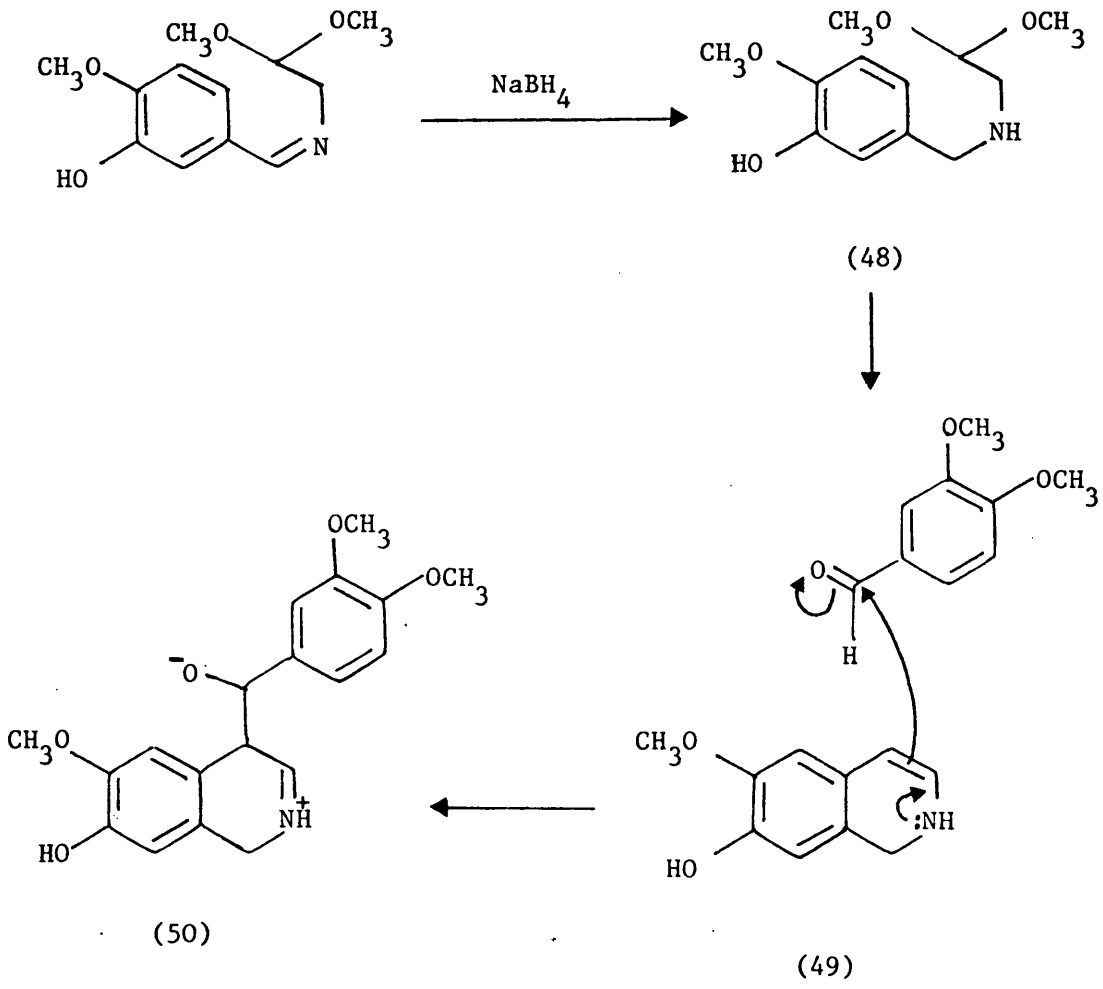
(46)

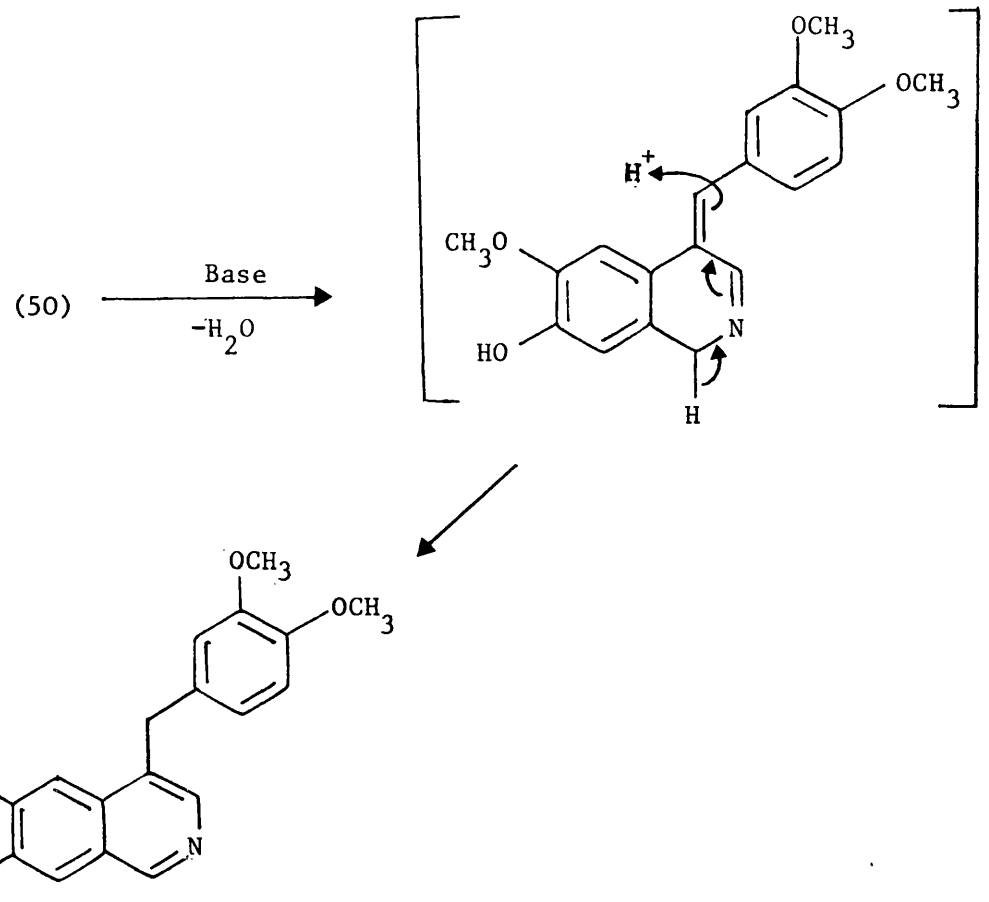
Reductive alkylation of the benzylamine (41) with formalin followed by the usual cyclisation yields the 2-methyl-1,2,3,4-tetrahydroisoquinoline (47).[40b]



(47)

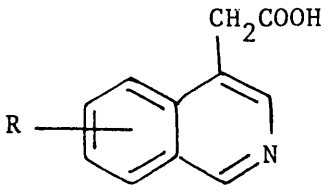
Bobbitt further extends his reaction[41] to incorporate a 4-benzyl substituent into the isoquinoline product by treating the amine (48), with a benzaldehyde and 6M hydrochloric acid. The first product is a 1,2-dihydroisoquinoline (49) which behaves as an enamine and reacts with the aldehyde to give, after dehydration of an intermediate carbinolamine, the 1,4-dihydroisoquinolinium salt (50). This product then isomerises to the fully aromatic isoquinoline (51) on base treatment at the end of the reaction.[42]





(51)

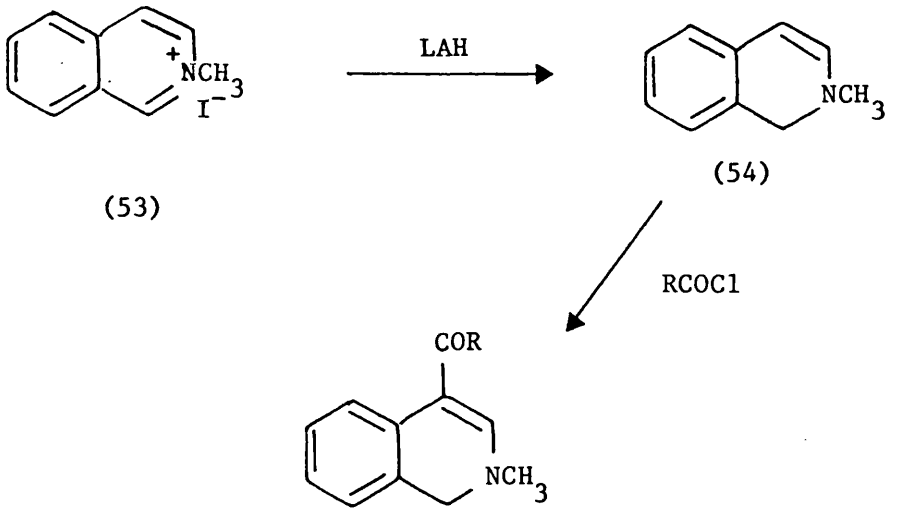
Other aldehydes can be used and glyoxalic acid, for example, affords the isoquinoline-4-acetic acid[43](52).



(52)

1,2-Dihydroisoquinolines can also be generated by reduction of isoquinoline salts with lithium aluminium hydride (LAH). These reactive species can then be treated with electrophiles such as aldehydes, alkyl halides or acyl halides to give 4-substituted isoquinolines.

As an example the methiodide (53) was reduced with LAH in ether to give 1,2-dihydro-2-methylisoquinoline (54). This was then treated with various acid chlorides in the presence of triethylamine to give 4-acyl-1,2-dihydroisoquinoline (55).



(53) (54) (55)

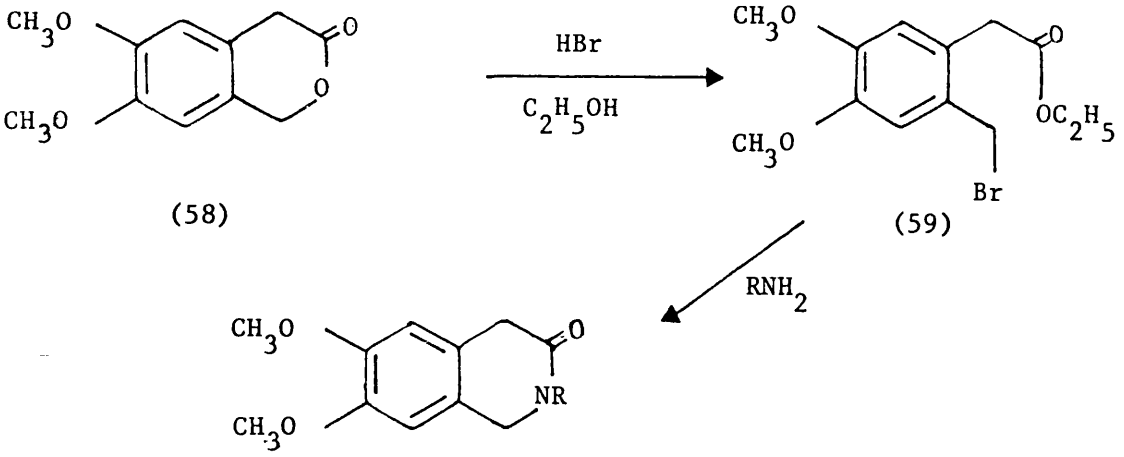
The latest improvement of the Pomeranz-Fritsch reaction is that announced by Watanabe.[44] Here a benzylamine (37) is treated with cold chlorosulphonic acid and cyclised to the isoquinoline (38) directly. This technique has been applied to isoquinolines substituted in the 1-, 6-, and 7-positions

to give yields ranging from 15% to 75%. In general, the productivity is best when the isoquinoline does not contain an alkoxyl substituent in either the 6- or 7-positions.

4. Synthesis involving the conversion of a 3-isochromanone (56) into a 1,4-dihydro-3(2H)-isoquinolinone (57).

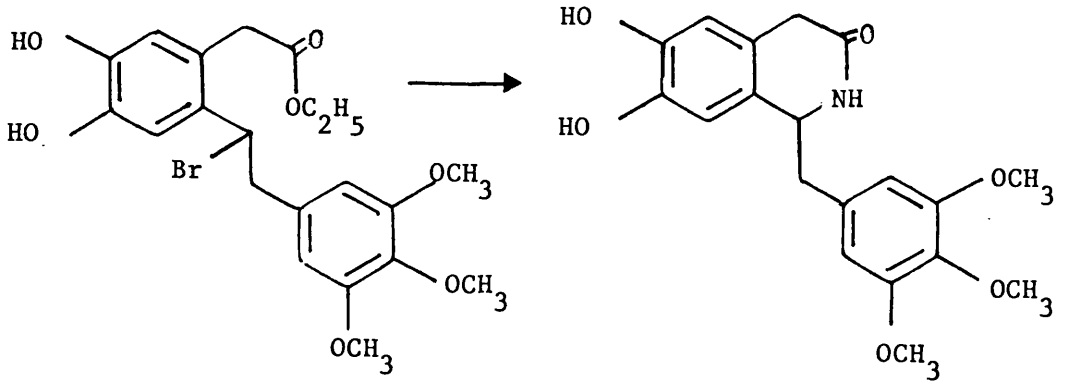
(56) (57)

Brossi[45] has effected the conversion of an isochromanone into an isoquinolinone by the action of an ethanolic solution of hydrogen bromide on the substrate (58). This gave the bromo-ester (59) which was then treated with a primary amine to form the isoquinolinone (60).



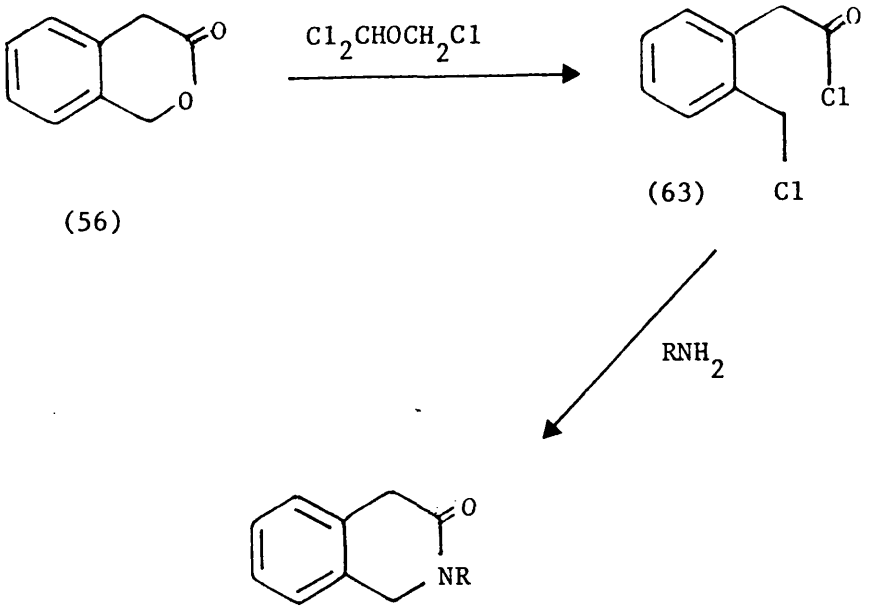
(58) (59) (60)

This method has also been used to prepare the 1-substituted isoquinoline (62)[46] by the action of ammonia on the corresponding bromo-ester (61).



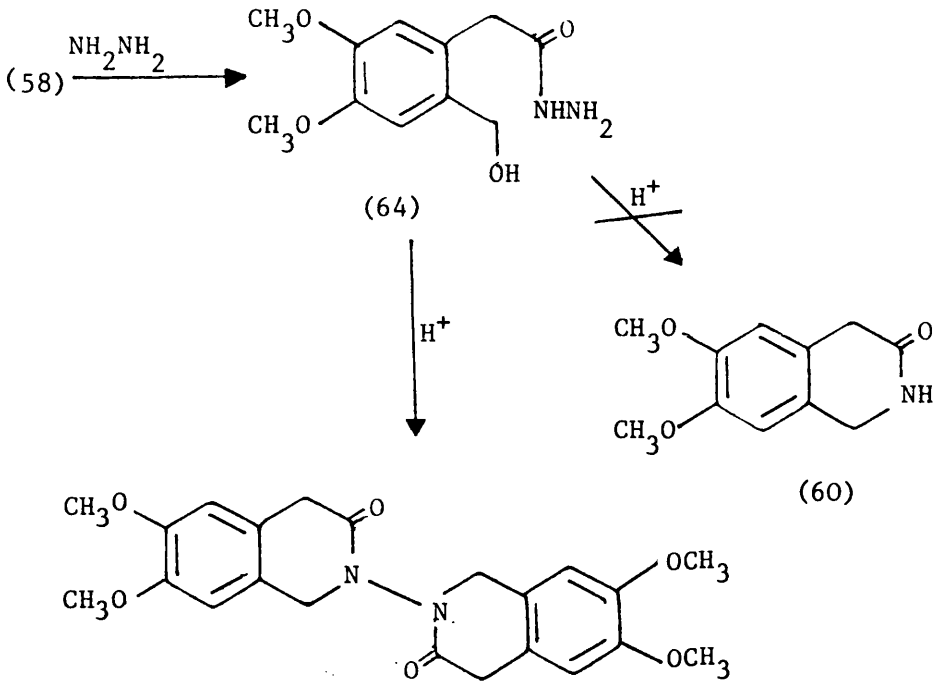
(61) (62)

A similar method[47] involved the action of dichloromethyl-chloromethylether on the isochromanone (56) which then gives the chloro-acid chloride (63). When heated in xylene under reflux conditions with a primary amine, this intermediate gave the isoquinolinone (57).



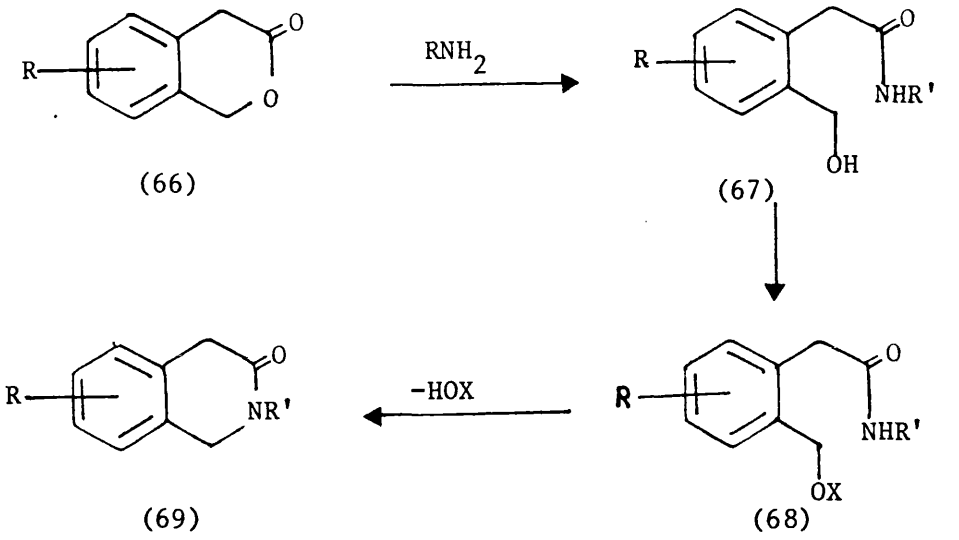
(56) (63) (57)

The only other method reported in this category, by Rosen and Popp[48], has as its first step the treatment of isochromanone (58) with hydrazine in ethanol. This formed the hydroxyhydrazide (64) which was then treated with dilute hydrochloric acid and was said to have produced the isoquinolinone (60). Subsequently it was demonstrated by Bird and Sainsbury[49] that the true product is the dehydrodimer (65) (see p.37).



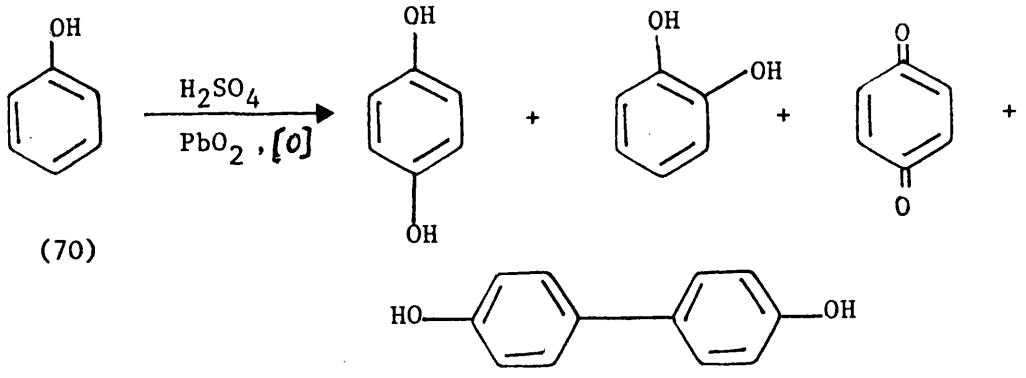
(65)

Obviously p-amines are the required reagents for the desired type of ring-opening reaction and Hoeft[47] reports three examples of this type of conversion. The one which involves the least severe conditions being the heating of an isochromanone (66) and a primary amine in xylene, thus yielding the corresponding amide alcohol (67) which may then be cyclised in two steps to the isoquinolinone (69).

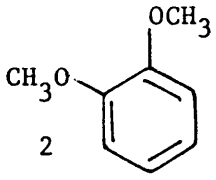


(vi) Electrochemical Oxidation of Arenes and Isoquinolines

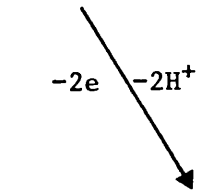
The electrochemical oxidations of isoquinoline derivatives fall into two sections, namely the oxidation of phenolic and non-phenolic compounds. So it is appropriate to consider the background to this work. Early reactions of phenols were carried out using lead dioxide anodes and a dilute sulphuric acid as the electrolyte. Since phenols are very easily oxidised, it is not surprising that a number of products form, some of which are intermolecularly coupled, and some not. For example, Fisher[50] who pioneered most of this work showed that the oxidation of phenol (70) gave the following products:

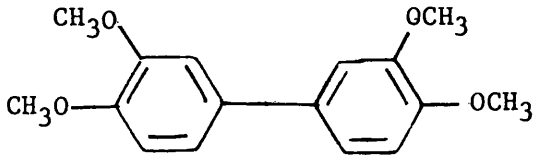


Covitz[51] has developed this same reaction to afford hydroquinone in over 90% yield, by strict control of the working potential. Later, Fichter[52] working with 1,2-dimethoxybenzene (71) and using either platinum or lead dioxide anodes demonstrated that the major product was the para-para coupled compound 3,3',4,4'-tetramethoxybiphenyl (72).



(71)

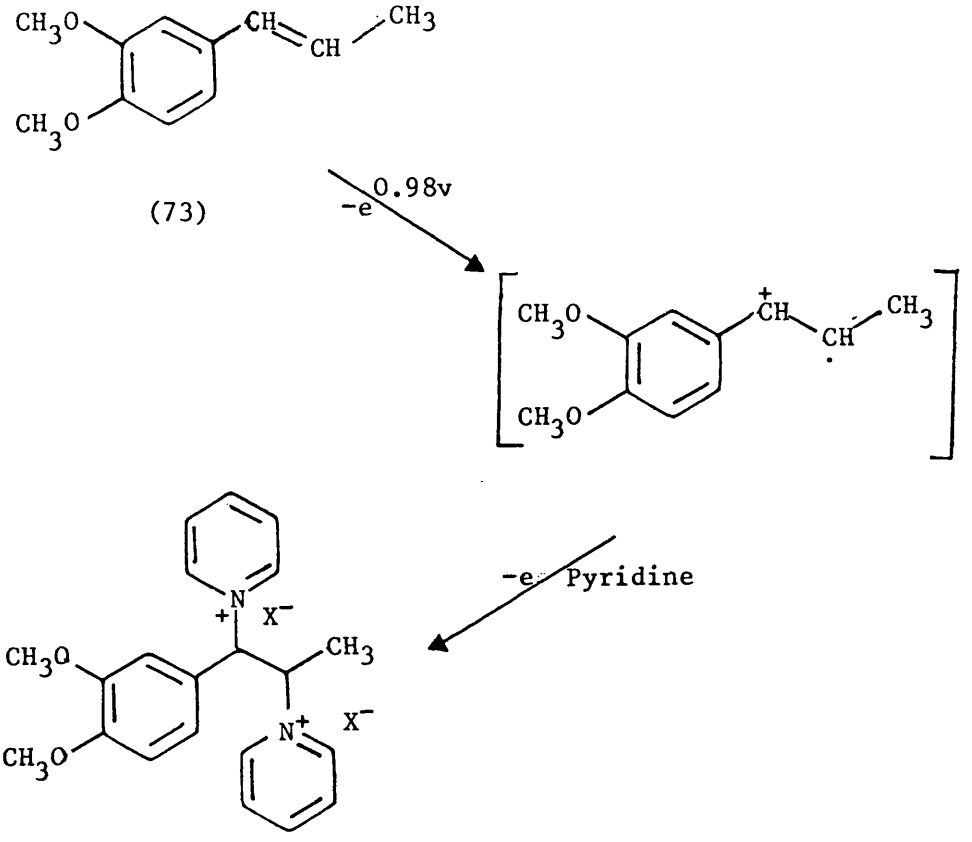




(72)

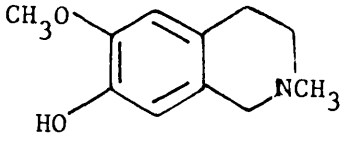
When styrenes are employed aryl-aryl coupling may be surplanted by reactions involving the side chain. For example, Pearl et al[53,54] have shown that the propenylbenzene (73) undergoes anodic oxidation to yield a cation radical and in the presence of pyridine other workers[55] have illustrated

that this species undergoes further oxidation and may be trapped as the dipyridinium salt (74).

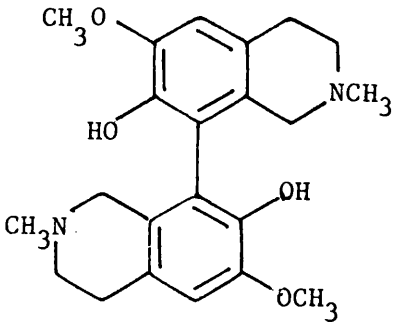


(74)

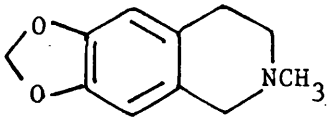
In recent years natural products particularly those based upon the isoquinoline system have received the attentions of electro-organic chemists. Bobbitt[56] has studied the anodic oxidation of corypalline (75) which then yields the dimer (76) in good yield. By contrast the methylenedioxy analogue (77) fails to enter into any coupling reactions under similar reaction conditions[57].



(75)



(76)



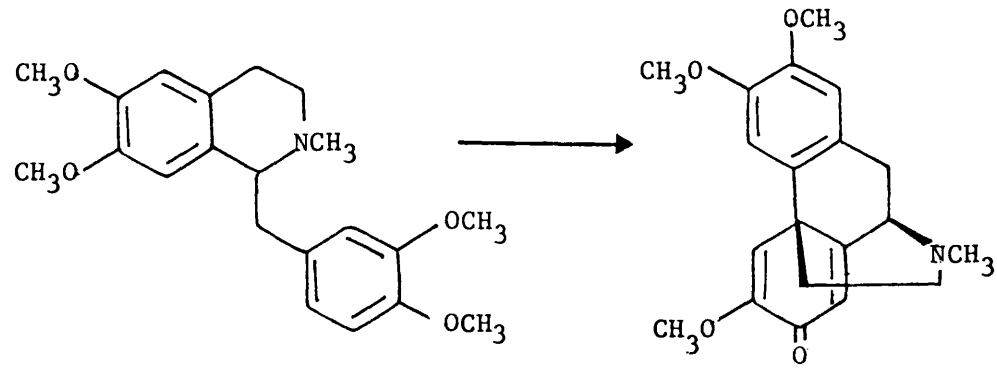
(77)

In general tetrahydroisoquinolines form stable redox-couples under electrochemical conditions due to ionisation of the nitrogen lone pair electrons, but, when steric conditions permit, this leads to nitrogen-carbon products.

In this thesis all the isoquinoline derivatives studied were non-phenolic and most contained the 3,4-dimethoxyphenyl group which has an oxidation potential of approximately +1.2 volts relative to SCE as the reference electrode.

The most widely studied reaction in the isoquinoline field is that of the intramolecular coupling of 1-benzyltetrahydroisoquinolines to give morphinandienones[58]. The electrooxidation of laudanosine (78) at +1.1 volts (vs. Ag/Ag^{+})

in an acetonitrile lithium perchlorate electrolyte system to give the O-methylflavinantine (79) in 52% is the best example of this type.



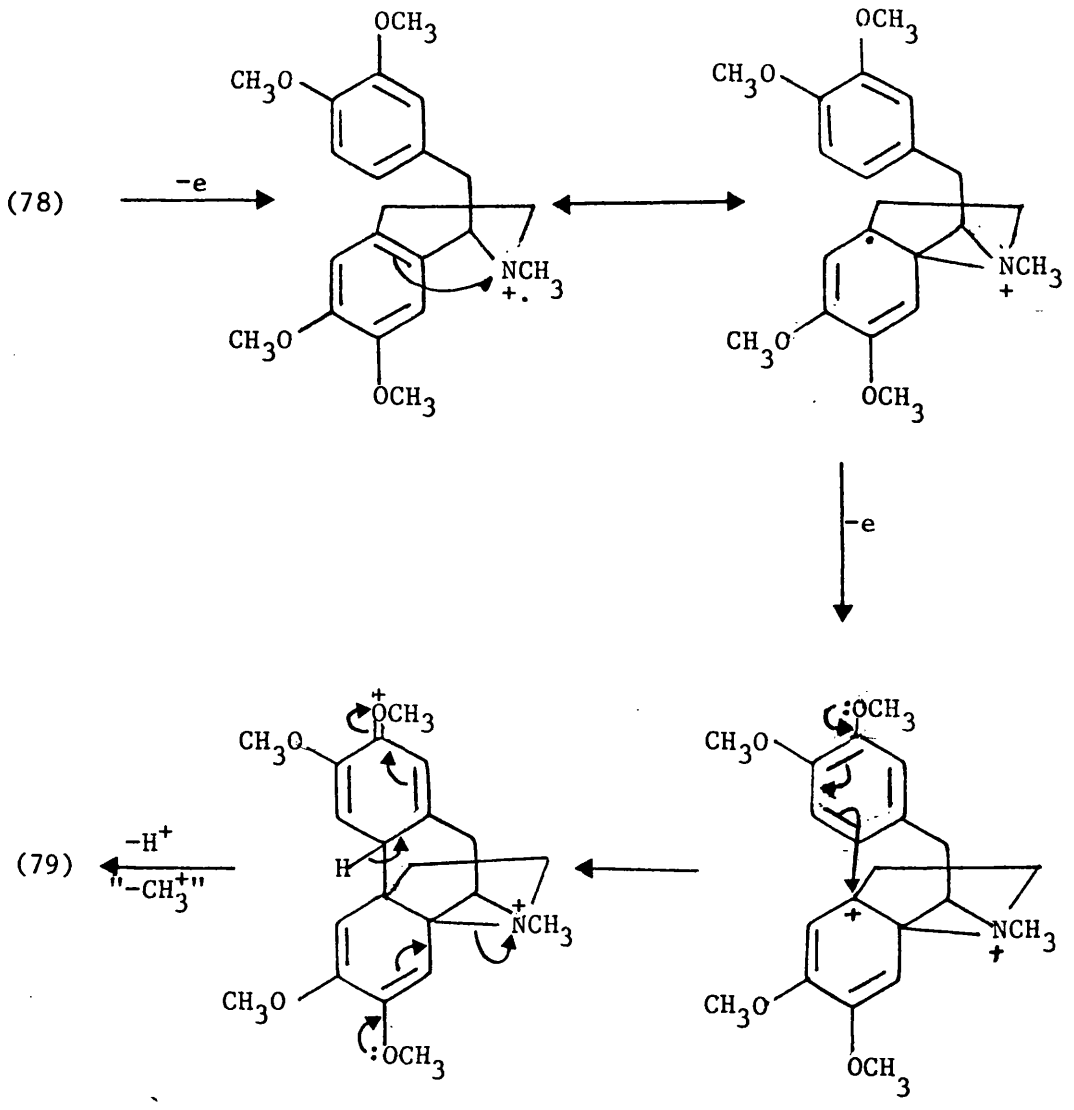
(78)

(79)

The mechanism of this process was considered to be a simple "eec" or "ece" coupling of the two aryl nuclei, but this ignored the fact that the first oxidation potential laudanosine (78) occurs at only +0.63 volts[58], an oxidation which must be attributed to the loss of electrons from the nitrogen atom. This anomaly was later resolved by the deployment of a mechanism (Scheme 4) which involves anchimeric assistance by the oxidized nitrogen atom aiding the formation of an aryl-aryl bonded intermediate.[59] The mechanism was said

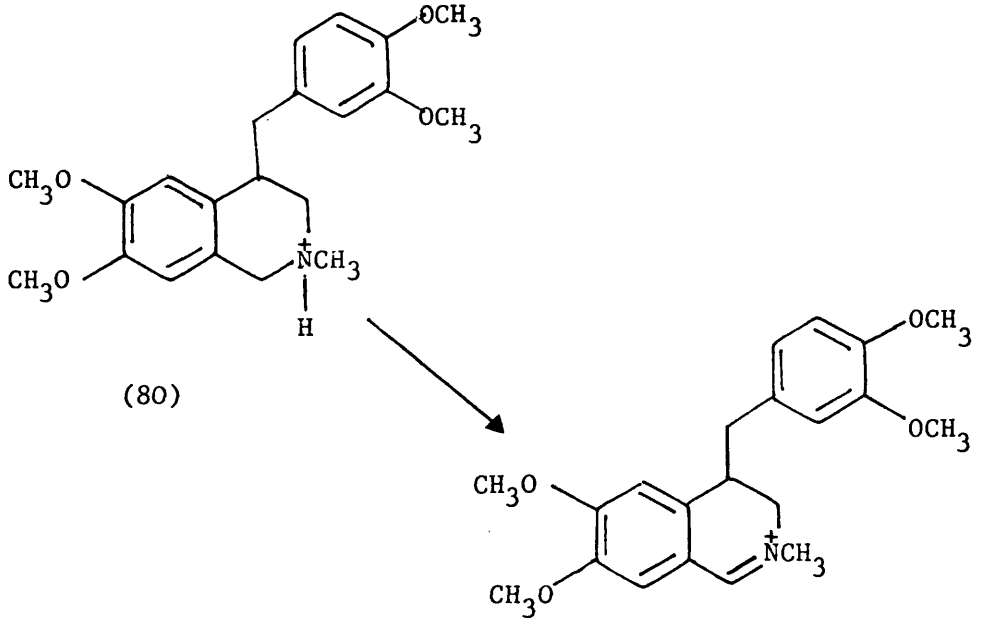
to be validated by the fact that substantial amounts of O-methylflavinantine (79) are produced even at electrode potential as low as +0.6 volts.

Scheme 4.



This mechanism has been disputed by Sainsbury et al[60], who have presented evidence to prove that the low potential reaction is in fact an example of an intermolecular electron transfer process in which the initial ion reacts with an molecule of the substrate to afford a second ion with the charge centred on an aryl nucleus. Details of this argument are outside the range of this introduction.

In the case of the 4-benzylisoquinolinium salt (80) oxidation gives the benzylidene species (81) and similarly anodic oxidation of 1-phenethyltetrahydroisoquinoline (82) gives rise

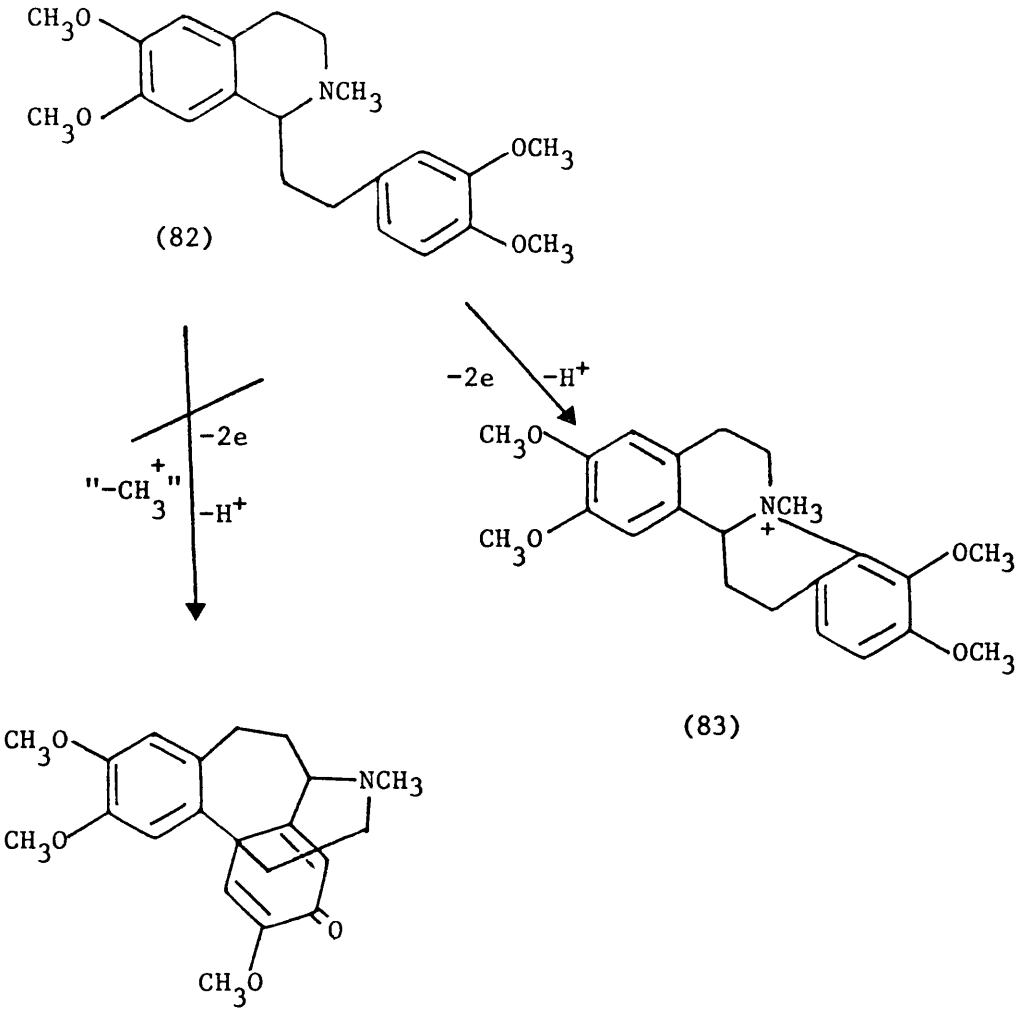


(80)

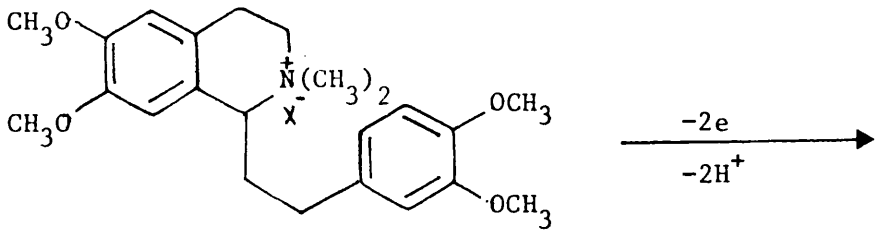
(81)

to the tetracycle (83)[61]. This product was not expected since it had been anticipated that the oxidation would give rise to the androcymbrine derivative (84) by a coupling

reaction route analogous to that observed in the case of laudanosine (for a discussion of the ether fragmentation process see p. 41).

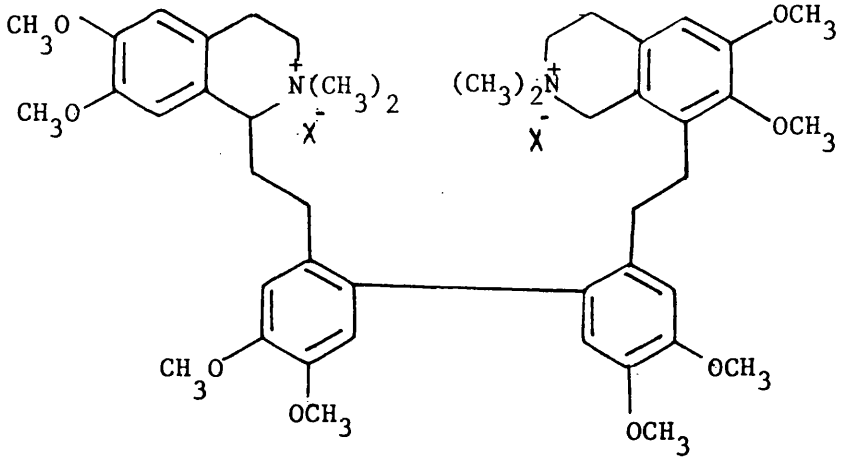


Oxidation of the methoperchlorate salt (85) of (82)[62] also failed to give a spirodienone, the dehydrodimer (86) being the only isolated product.



(85)

X = ClO_4



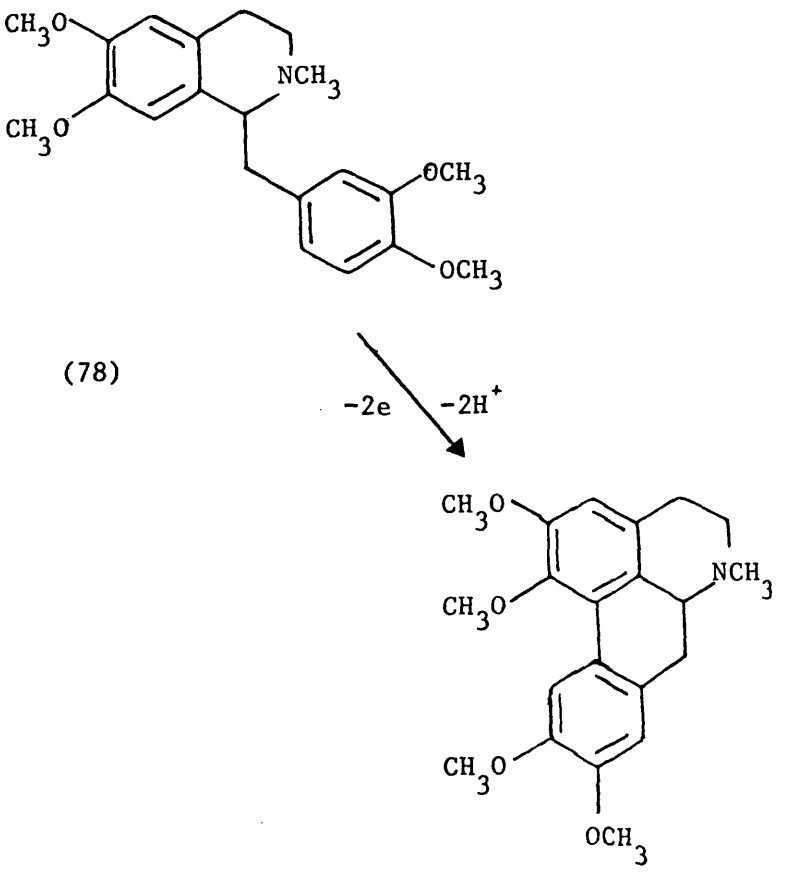
(86)

The reasons for these various coupling modes are not immediately obvious and an investigation of them forms part of this thesis.

The Use of Chemical Oxidants in Coupling Reactions

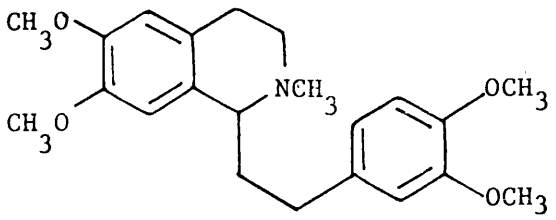
In the past few years there has been an upsurge in the use of chemical single electron transfer reagents to effect the non-phenolic oxidative coupling of aryl systems. The two most important reagents to have emerged are vanadium(V) oxyfluoride and thallium(III) trifluoroacetate. These reagents can act as one electron oxidants and so mimic anodic reactions by the generation of radical cations.

An example of the use of vanadium oxyfluoride is the oxidation of laudanosine (78) to glaucine (87). The reagent is used in trifluoroacetic acid (TFA) solution[63]. Similarly it has been observed that oxidation of 1-phenethyltetrahydroisoquinoline (82) with vanadium oxyfluoride gives the homoaporphine (88)[64] rather than the salt (83). Undoubtedly complexation with the reagent and the nitrogen atom's lone pair accounts for the latter regioselectivity, but why glaucine the product of an ortho-para C-C-coupling is formed in preference to O-methylflavinanthine is still a mystery (see, for example, p.43).

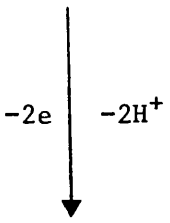


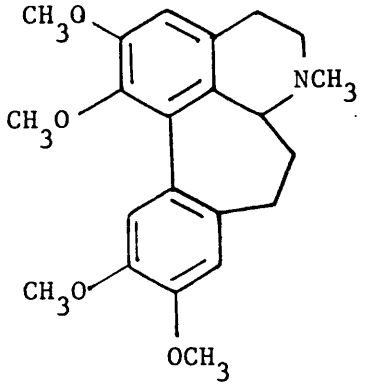
(78)

(87)



(82)



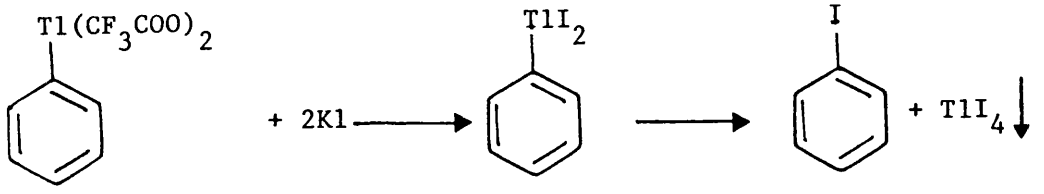


(88)

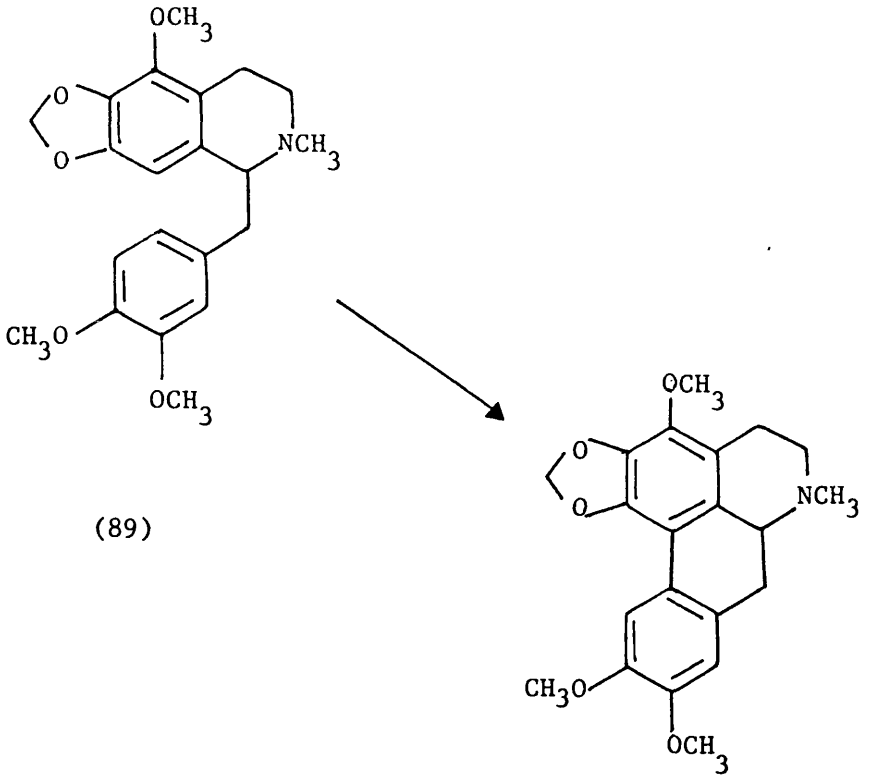
The use of thallium trifluoracetate (TTFA) presents a problem in so far as metalation of an aryl ring[65] and oxidation to the radical cation are competing reactions, but for aryl rings with low oxidation potentials, such as a dimethoxyphenyl ring, the one electron oxidation reaction predominates and metalation is only a minor event. In some cases, however, metalation is an advantage and it has been

used in the synthesis of aryl iodides from arenes of relatively high ionisation constants (Scheme 5).[66]

Scheme 5.



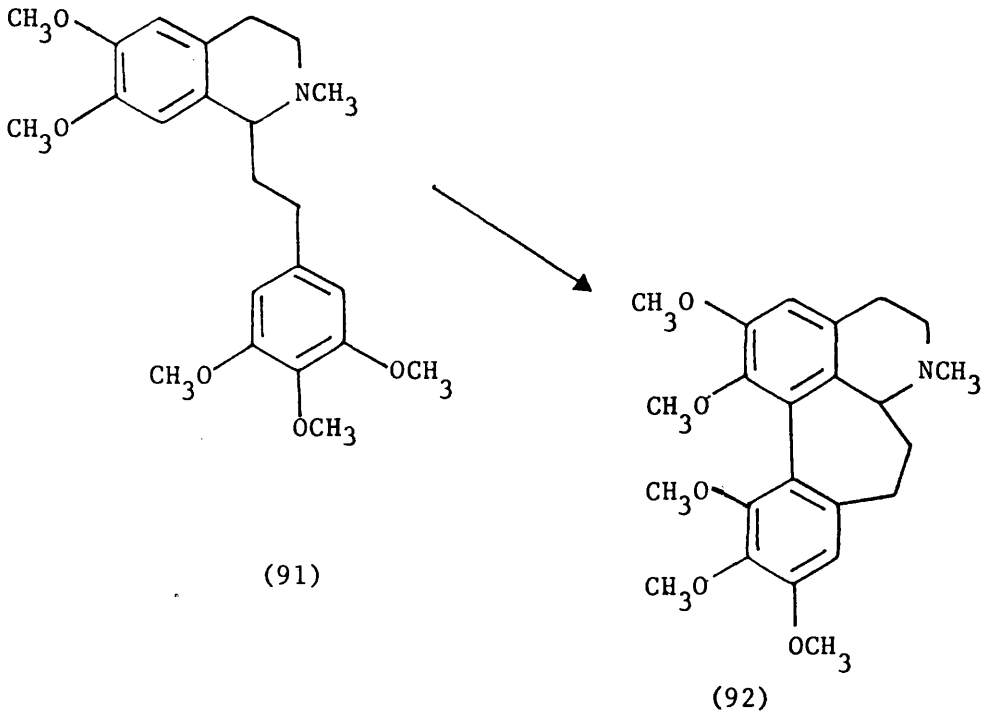
More recently chemically induced one electron removal reactions have been applied to the synthesis of biaryls[67] and intramolecular oxidative coupling reactions in general. Many of the reactions involve phenolic substrates and in these cases the phenoxonium ion plays an important role in the presumed mechanistic sequence. TTFA can also be applied to the coupling reactions of non-phenolic substrates. For example, treatment of the 1-benzyltetrahydroisoquinoline (89) with TTFA in acetonitrile and carbon tetrachloride at $-40C^{o}$ in the presence of a catalytic amount of boron trifluoride etherate gives the alkaloid ocoteine (90)[68].



(89)

(90)

Similarly, treatment of the 1-phenethyltetrahydroisoquinoline (91) with TTFA in trifluoracetic acid and dichloromethane yielded O-methylkreysigine (92).[69]



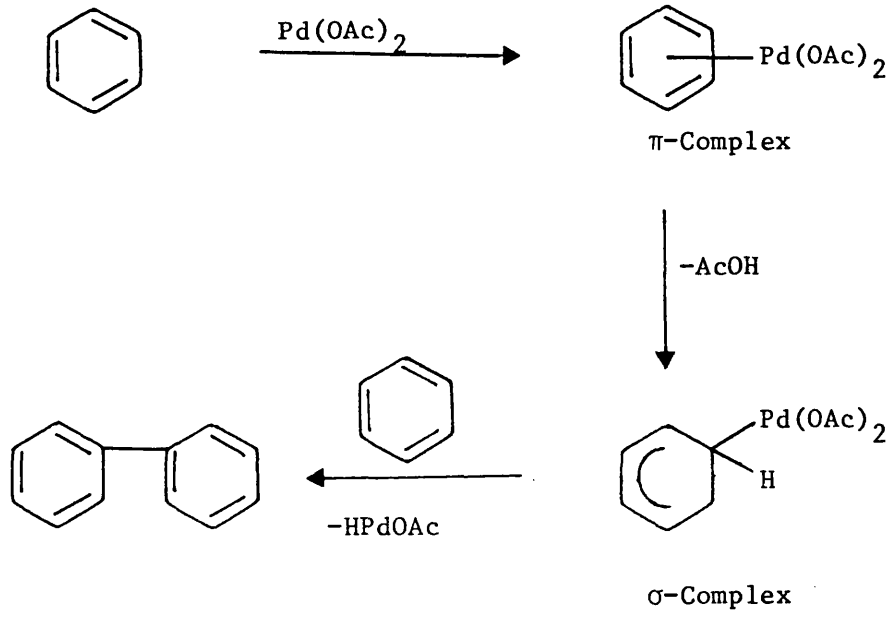
(91)

(92)

There is an obvious discrepancy here with the results of anodic oxidation (see p. 43), but again it is likely that coupling to the nitrogen atom is precluded by complexation of the reagent to the lone pair electrons.

Another oxidant which has been used in coupling reactions is palladium(II) acetate. The mechanism which takes place with this reagent involves palladation of an aromatic ring to form a complex which is easily decomposed to give a biaryl[70]. The first use of palladium acetate in reactions of this type was in the synthesis of biphenyl from benzene (Scheme 6)[71].

Scheme 6.

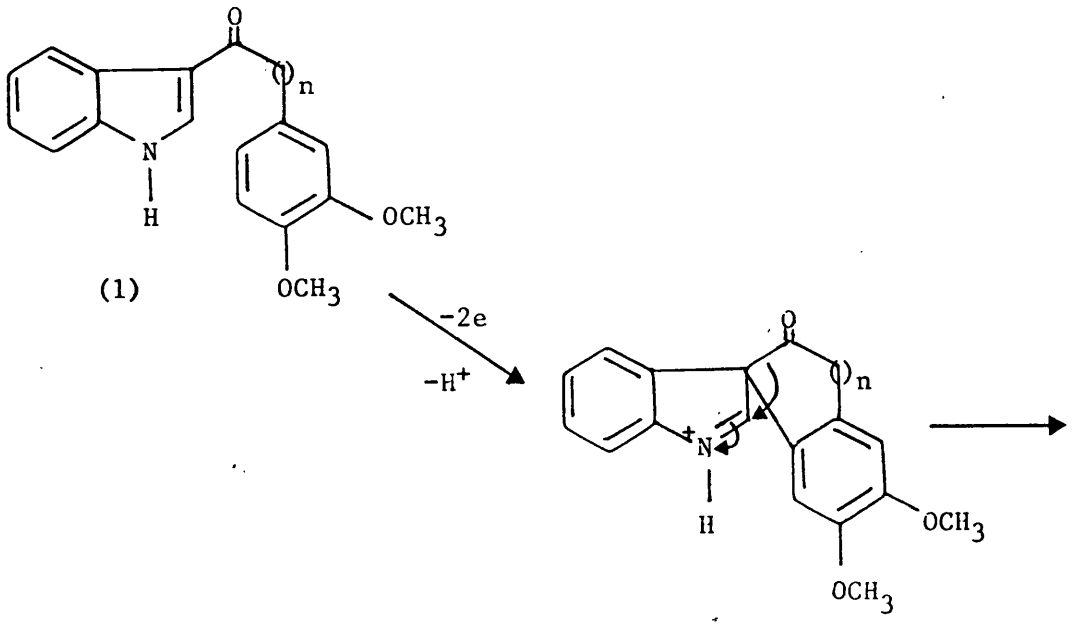


DISCUSSION

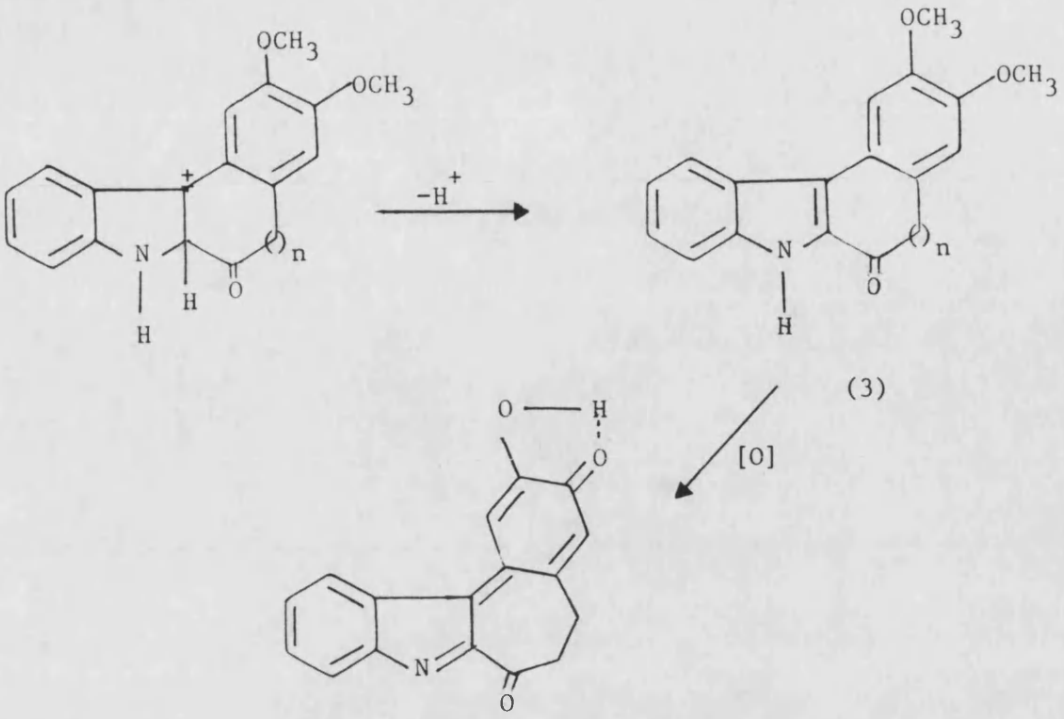
(i) Background

The report by Sainsbury and Powell[1], that the electrochemical and chemical oxidative cyclisation reactions of some indole and isoquinoline derivatives appear to favour 6-membered transition states rather than their 5-membered counterparts, explains a number of anomalous results obtained earlier. For example, Wyatt[2] showed that the 3-arylpropanoylindole (1, n = 2) when electrolysed gave the quinone (4), whereas the lower homologue (1, n = 1) did not undergo intramolecular cyclisation[3].

The quinone (4) is obviously the product of over-oxidation of the indole (3, n = 2) and thus it would appear that the initially formed radical cation attacks position-3 of the indole nucleus giving a spiro-intermediate (2) which then ring expands in a predictable manner.

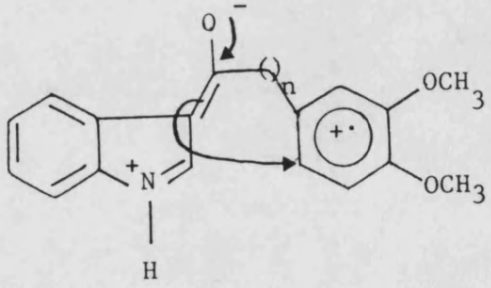


(1) (2)



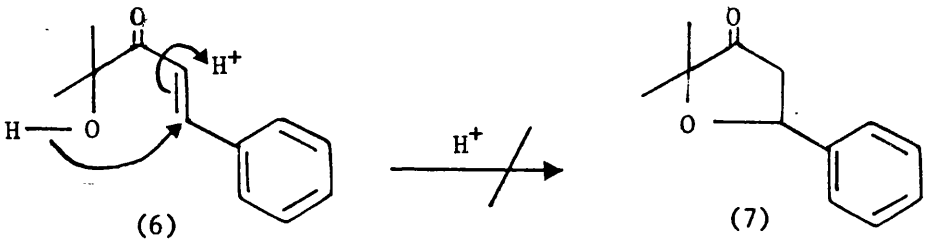
(4)

The intermediate (2, n = 2) is produced by a six-membered ring forming process whereas its lower homologue would clearly require a five-membered ring to form in the intermediate (2, n = 1). From this evidence Sainsbury[4] drew attention to the fact that the Baldwin rules[5] provide a probable explanation for these results. Thus the cyclisation of the radical cation (5, n = 2) may be regarded as a 6 endo-trig process, whereas that of the lower analogue (5, n = 1) would be an example of a 5 endo-trig reaction which is thus kinetically disfavoured.

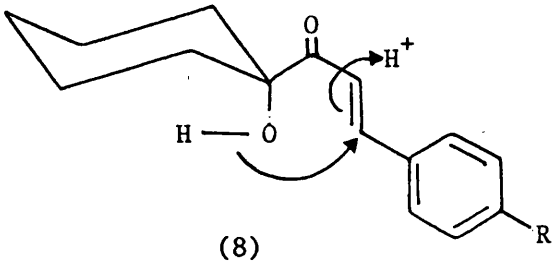


(5)

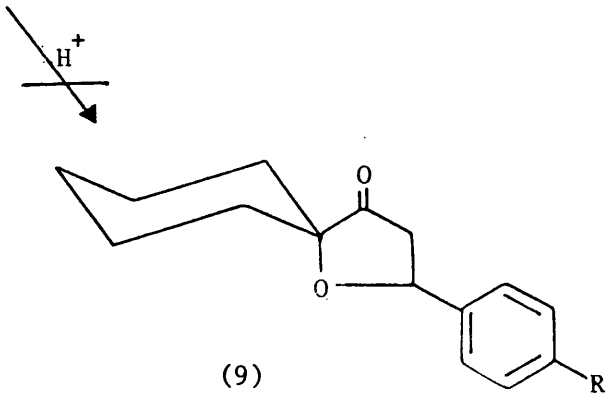
In Baldwin's[6,7] original work he showed that all attempts to cyclise the hydroxy-enones (6 and 8) to the lactones (7 and 9) respectively failed, despite the fact that electronically the enones were quite capable of undergoing intermolecular nucleophilic attack at the β-position of the enone chromophores.



(6) (7)



(8)



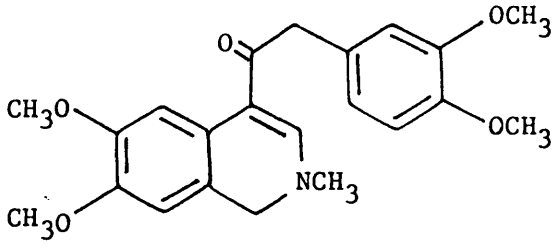
(9)

R = (H, OCH_3)

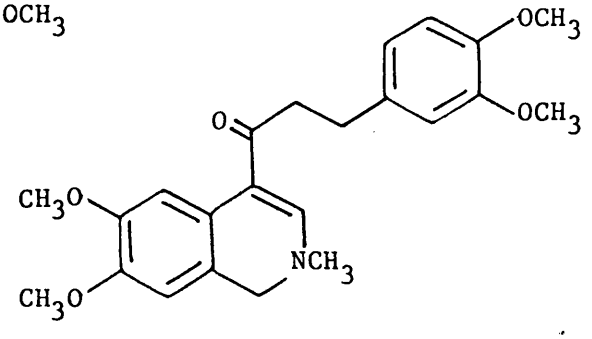
It was argued therefore that the geometries of the transition states leading to the furanones (7 and 9) were difficult to attain; i.e. the angles needed to develop the attack of the hydroxyl lone pair on the enone system were not reconcilable with those to be found in the products. Hence extra energy would be necessary to force the reactions to completion and thus they become disfavoured with respect to other intermolecular processes in which the nucleophile is free to approach at the correct angle.

Baldwin and his colleagues were then able to demonstrate that when a six-membered ring was forming at a trigonal (sp^2) centre, the natural bond angles of the product were, also being created and such reactions were "allowed".

Powell and Sainsbury[8] illustrated the generality of these rules to other electrochemical reactions by showing that only the higher of the two homologues (10 and 11) underwent intramolecular anodic cyclisation.

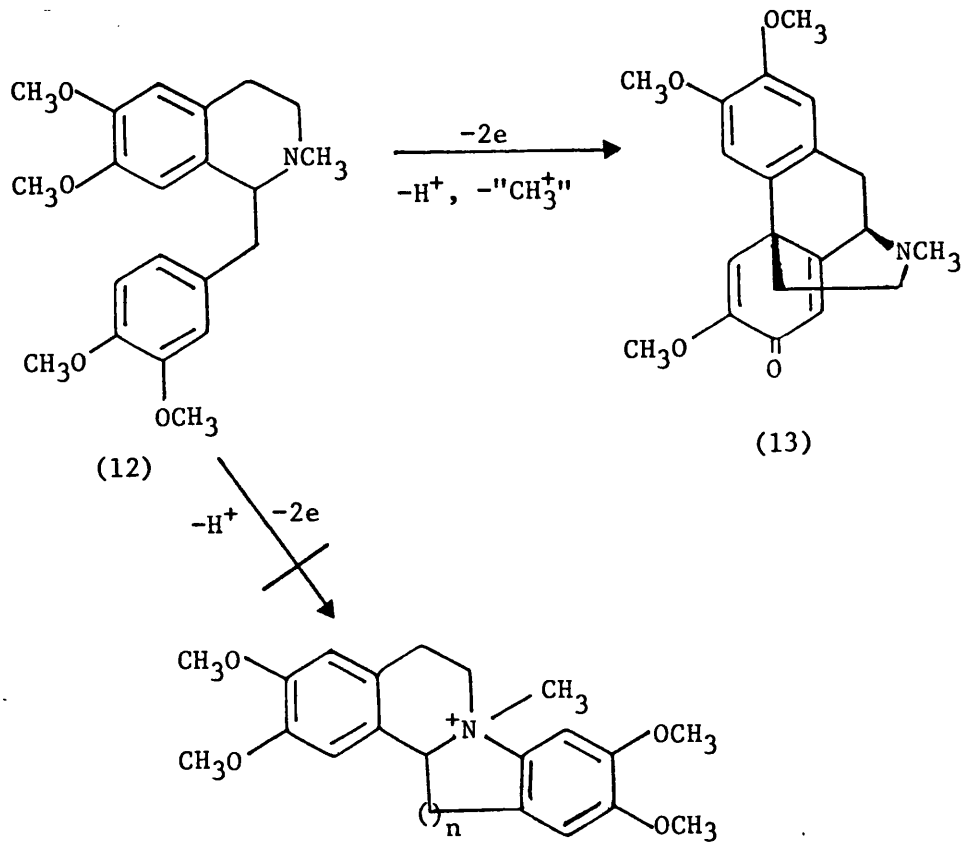


(10)

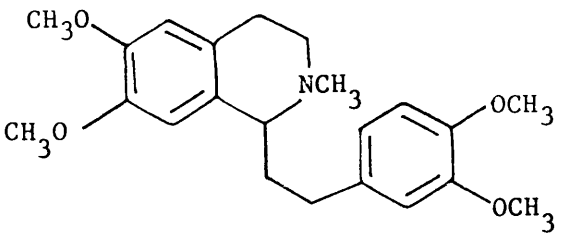


(11)

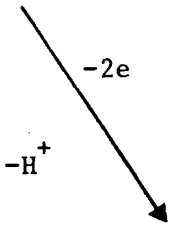
Some other examples are the alternative cyclisations of the 1-benzyl and 1-phenethyl isoquinolines (12) and (14) respectively. The first yields O-methylflavinantine[9,10] (13) by 6-endo-trig attack at C-8a whereas the latter gives the salt (15, n = 2) through ring formation on to the nitrogen atom of the heterocycle.[11] In the first case, although the lone pair electrons on the nitrogen atom are the easiest to ionise, attack at this site would create a five-membered ring (cf. 15, n = 1), so the reaction is directed to an alternative position. Such a problem does not exist in the higher homologue (14) and now the cyclisation proceeds to form an N-C bond.

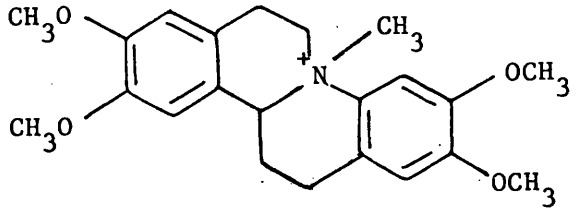


(12) (13) (15)



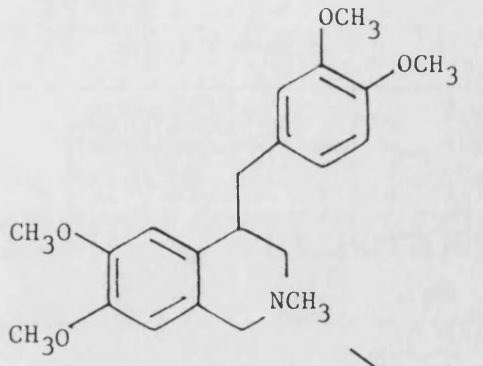
(14)



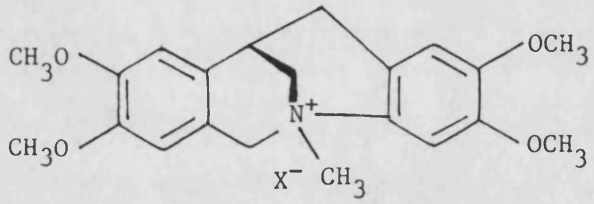


(15, n = 2)

Similarly Powell[12] showed that when the 4-benzyltetrahydroisoquinoline (16) was oxidised, it produced the salt (17), again through a 6-endo-trig process, but when the 4-phenethyl analogue (18) was electrolysed cyclisation gave the tetracycle (19). This last structure may be an example of an allowed 7-endo-trig reaction, or perhaps it requires indirect attack on to C-4a followed by a rearrangement, in which case, of course, it remains a 6-endo-trig process.

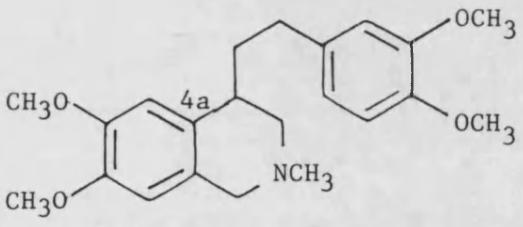


(16)

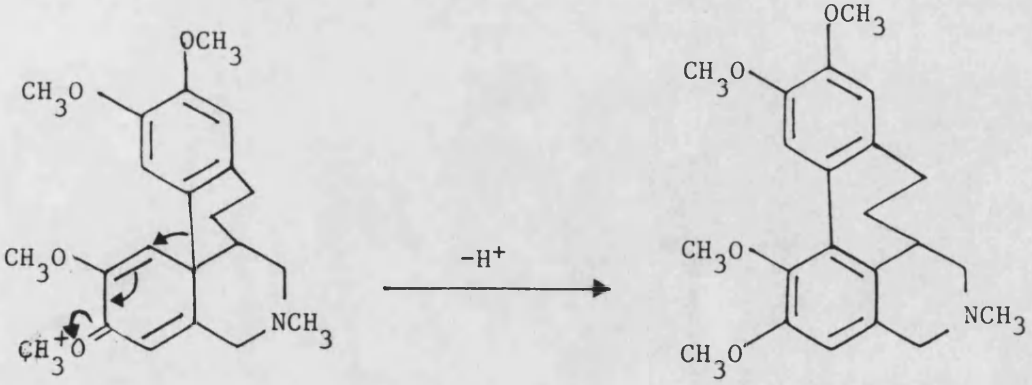


X = (ClO_4, CF_3CO_2)

(17)



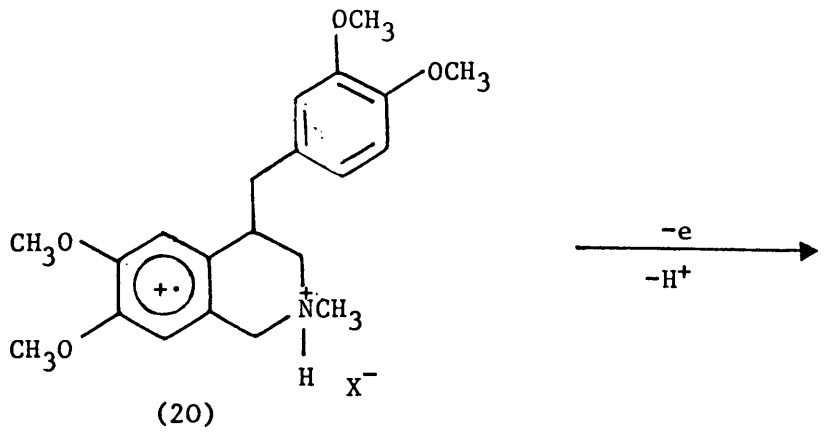
(18)



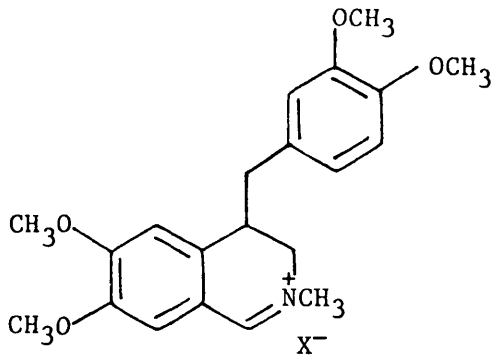
(19)

If acidic conditions are employed in the oxidation of the 4-benzylisoquinolines (16) or if chemical oxidants such as vanadium oxytrifluoride[13] are employed, the formation of the salt (17) is inhibited. In this case the lone pair electrons on the nitrogen atom are either protonated or complexed by the reagent and now the initially formed radical cation may no longer cyclise unless via an unfavoured transition state (see p. 52).

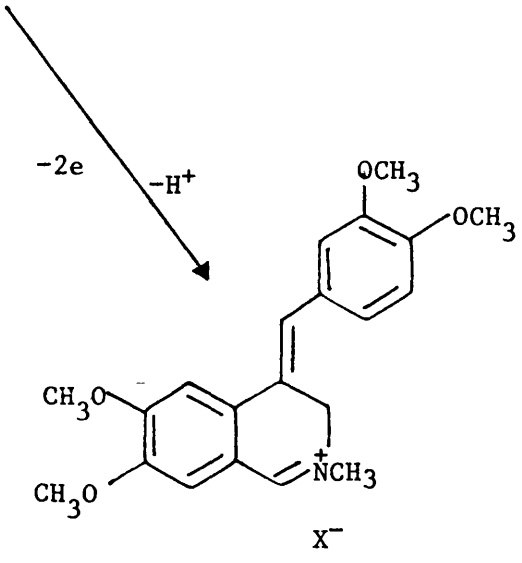
In practice the 3,4-dihydroxyisoquinolinum salts (21)[14,15] and (22) are produced (depending on the anode potential) through deprotonation and further oxidation of the radical cation (20). Some dehydro dimer (23) resulting from ionisation of the π-system of the 4-benzyl substituent alone is also produced.



(20)

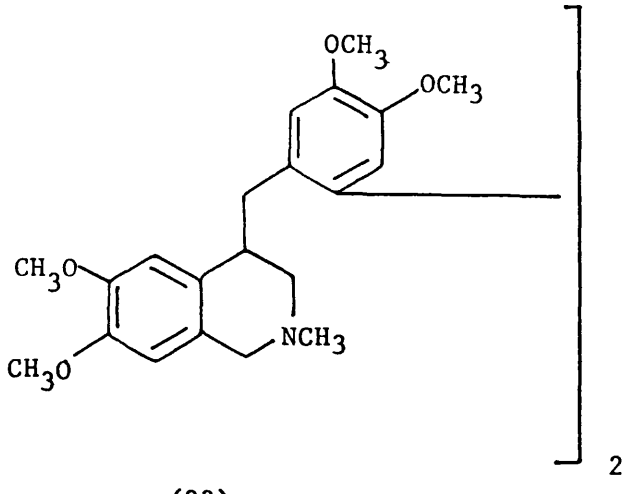


(21)



X = CF_3CO_2

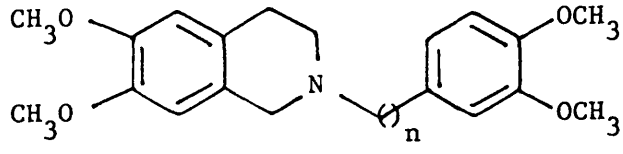
(22)



(23)

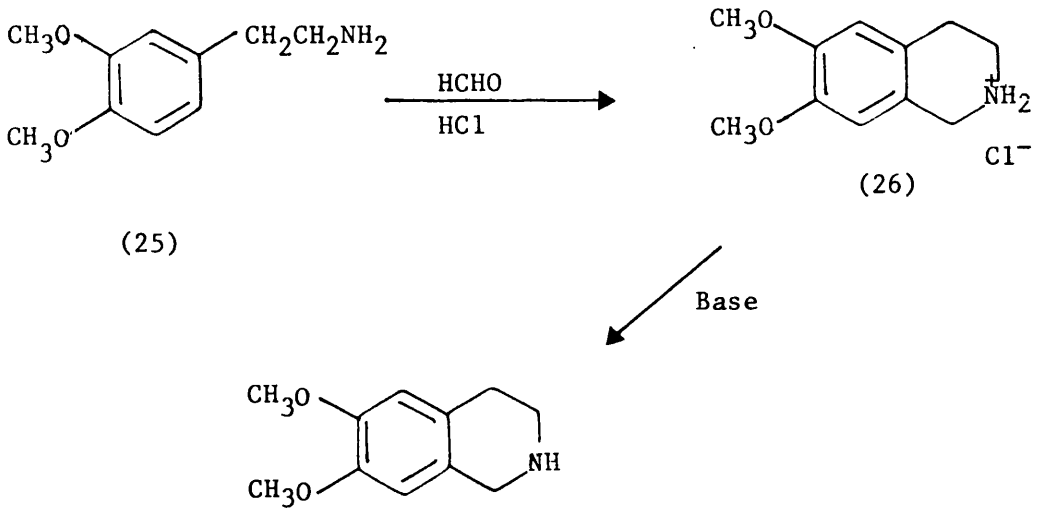
(ii) The oxidation of N-aralkyltetrahydroisoquinolines

The new work to be described in this thesis commenced with an investigation of the oxidative behaviour of N-aralkyltetrahydroisoquinolines. Would these further illustrate the cyclisation preferences described above? It was decided to prepare the homologues (24, n = 1) and(24, n = 2) and to study their anodic oxidation.



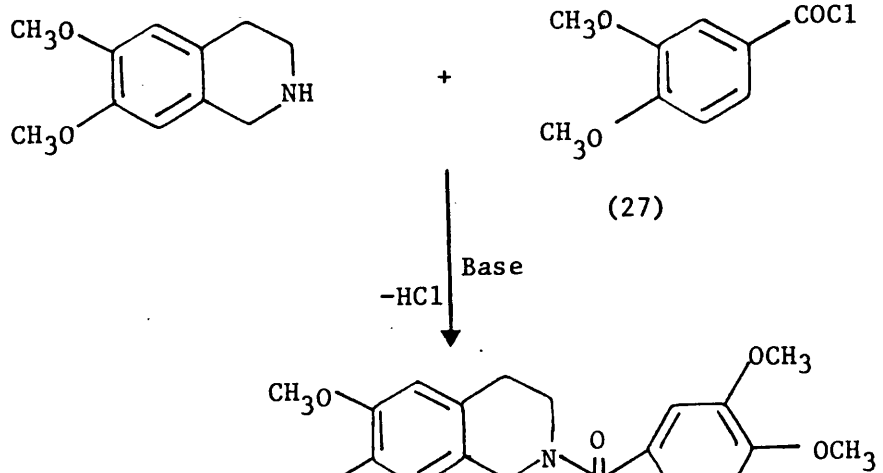
(24)

The required starting compounds were prepared by classical means: thus 2-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (24, n = 1) was synthesised by reaction of 6,7-dimethoxytetrahydroisoquinoline (obtained by a Pictet Spengler[16,17,18] reaction from the phenylethyl amine (25) and formaldehyde in the presence of hydrochloric acid.). This compound (26) was basified and treated with 3,4,dimethoxybenzoyl chloride (27)[19], to give the amide (28) which on reduction with lithium aluminium hydride afforded the required substrate.



(25)

(26)



(27)

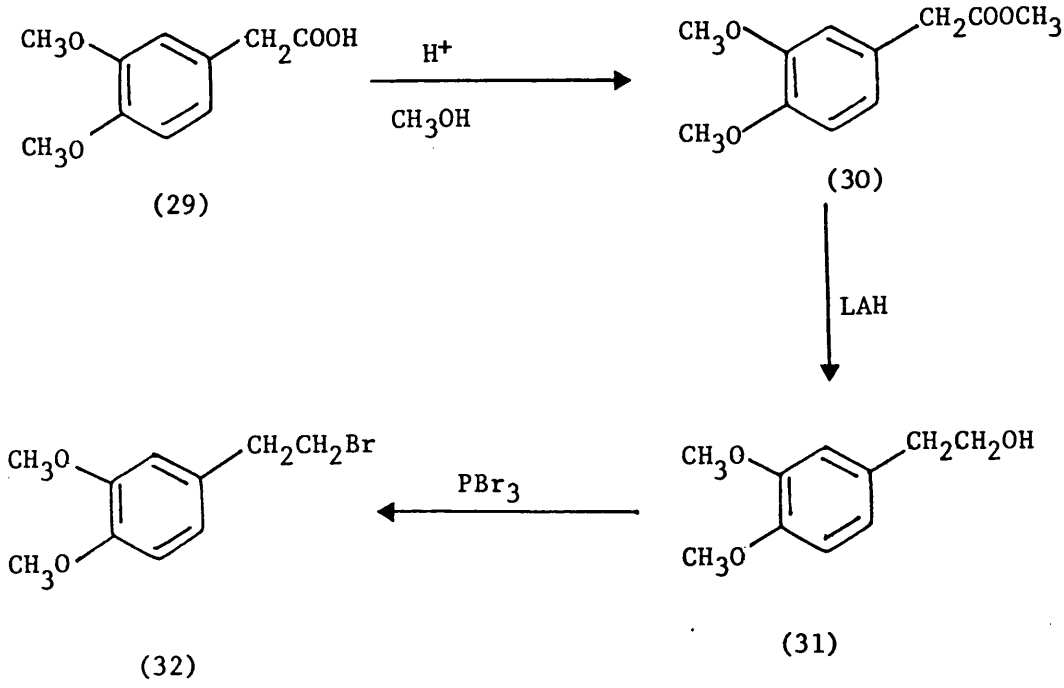
(28)

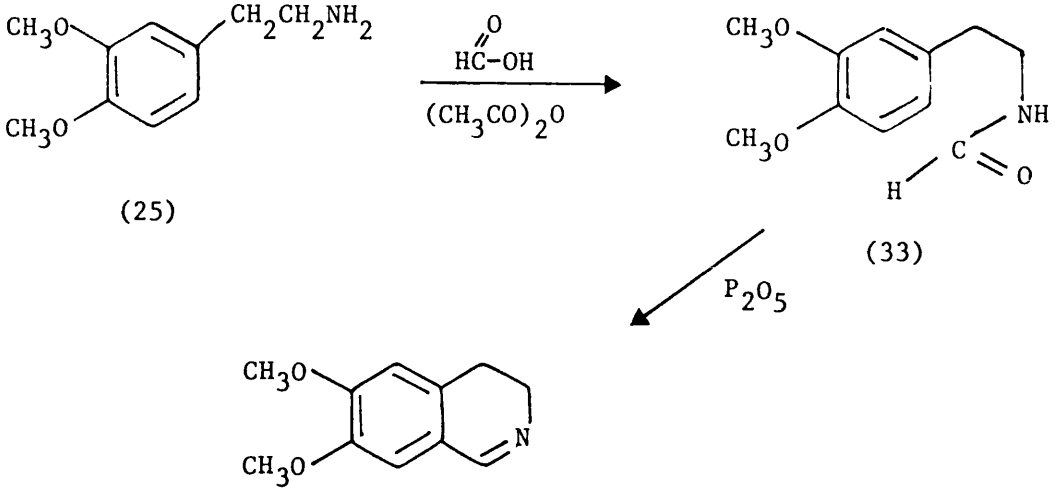
(24, n = 1)

The higher homologue (24, n = 2) was formed[20] by combining 3,4-dihydro-6,7-dimethoxyisoquinoline (34) and 3,4-dimethoxyphenylethylbromide (32) to give the salt (35)[21,22], and then reducing this product with sodium borohydride.[23]

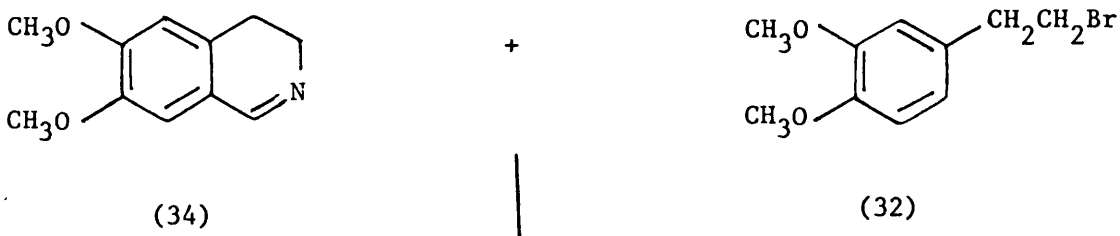
For this synthesis the alkyl bromide (32) was prepared in three steps from homoveratric acid (29) by: (a) esterification, (b) reduction of the ester[24] (30) to the corresponding alcohol (31), and (c) treatment of the alcohol with phosphorus tribromide.[21]

3,4-Dihydro-6,7-dimethoxyisoquinoline (34) was synthesised by the method of Späth and Polgar[25], i.e. from homoveratrylamine (25), acetaldehyde and formic acid, followed by cyclisation of the resultant N-formyl compound (33) with phosphorus pentoxide.[26]

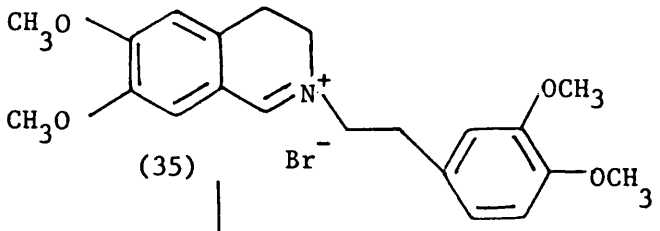




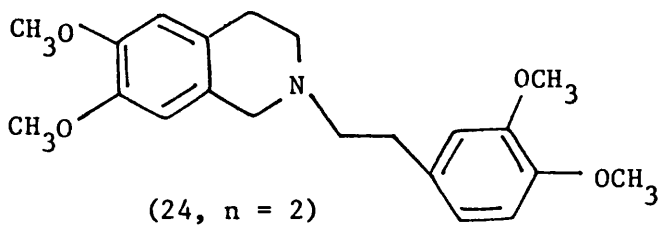
(25) (33) (34)



(34) (32)



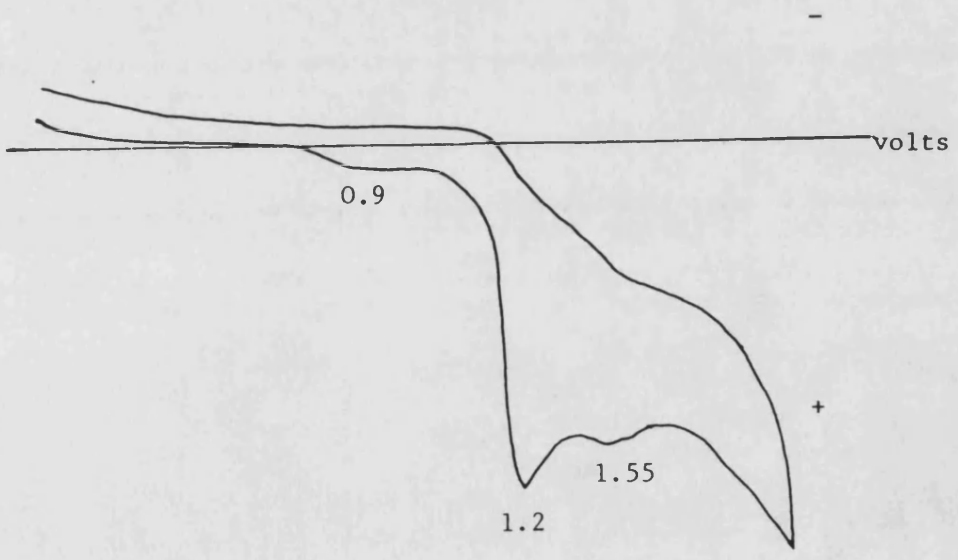
(35)



(24, n = 2)

The cyclic voltammogram (Figure 1) of the lower homologue (24, n = 1) shows three oxidation waves at +0.9v, +1.2v and +1.55v. The first ionisation is due to the loss of an electron from the nitrogen atom and the second is an electron loss from one of the two dimethoxylated aromatic rings. The origin of the third wave must be a further electron loss, probably from the π-system of the other aromatic nucleus of the now charged substrate.

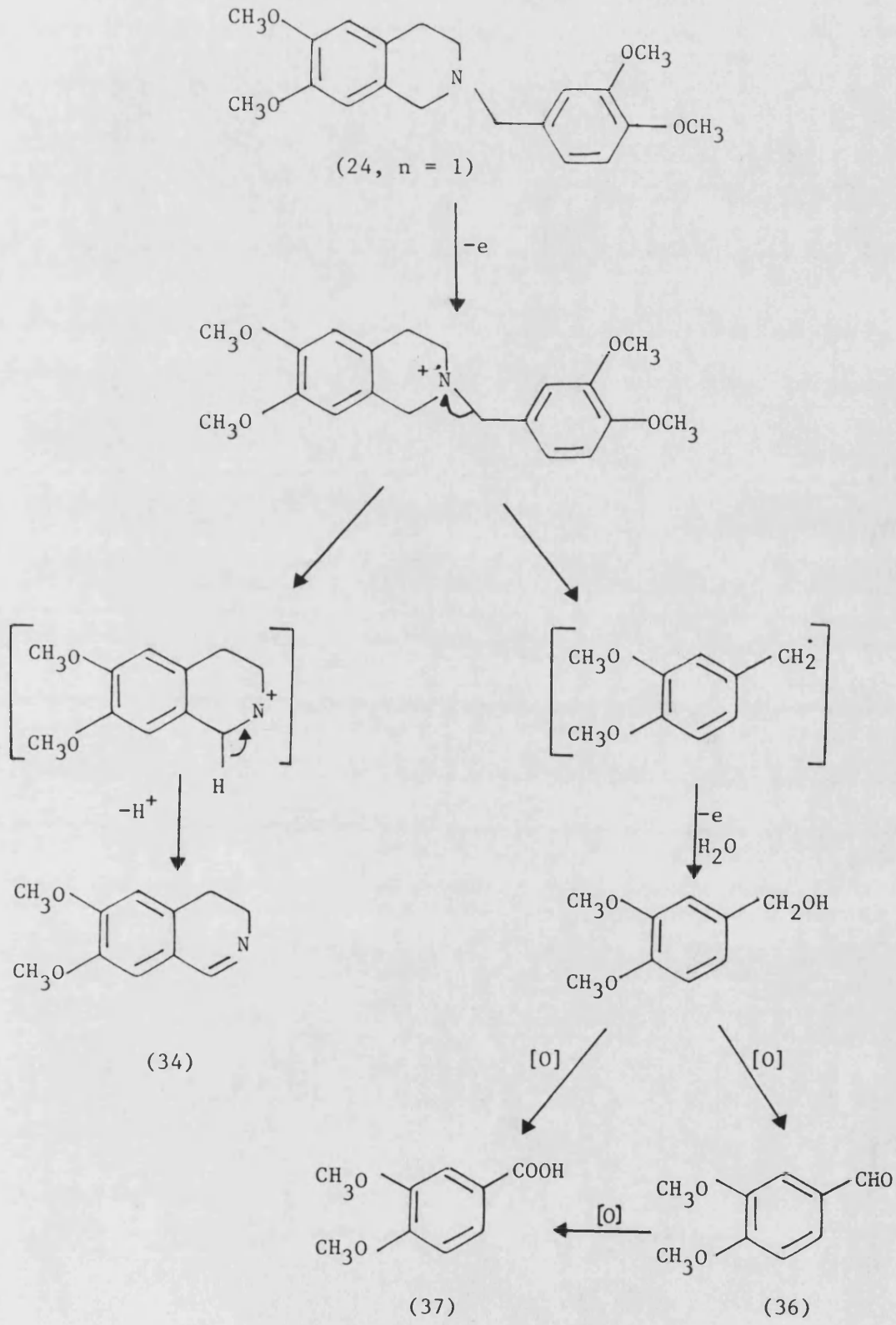
Figure 1. Cyclic voltammogram of N-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (24, n = 1).



A consideration of the shape of the curve (Figure-1) suggests that an immediate reaction is occurring but there are no obvious reduction peaks which is disturbing! In fact, when a preparative scale reaction was carried out at an anode potential of +1.1v, and until 2.2F mol^{-1} of charge had been consumed, only 3,4-dimethoxybenzaldehyde (36), 3,4-dimethoxybenzoic acid (37) and 3,4-dihydro-6,7-dimethoxy-isoquinoline (34) had formed. Clearly ionisation at nitrogen leads to fragmentation of the nitrogen-carbon bond probably as shown in Scheme-1, and this is followed by further oxidation of the scission products.

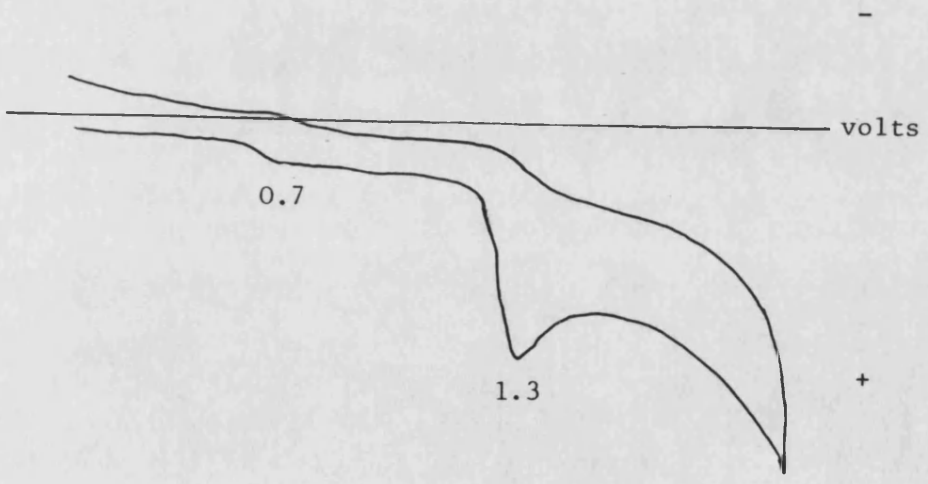
The identity of the 3,4-dihydroisoquinoline (34) was confirmed by comparison with the sample prepared earlier.

Scheme-1



A cyclic voltammogram (Figure-2) was also obtained for the higher homologue (24, n = 2) and in this case ionisation of the nitrogen lone pair electrons occurs at a more usual anode potential of +0.7 volts, and now there is indication that the process is reversible. Additionally the ionisation of one (or both) of the dimethoxylated ring systems at ≃ +1.3 volts is reversible to some extent. (The discrepancy between the first ionisation potentials of the two N-aralkyl-tetrahydroisoquinolines is noteworthy, but it is also a feature we are, as yet, unable to explain).

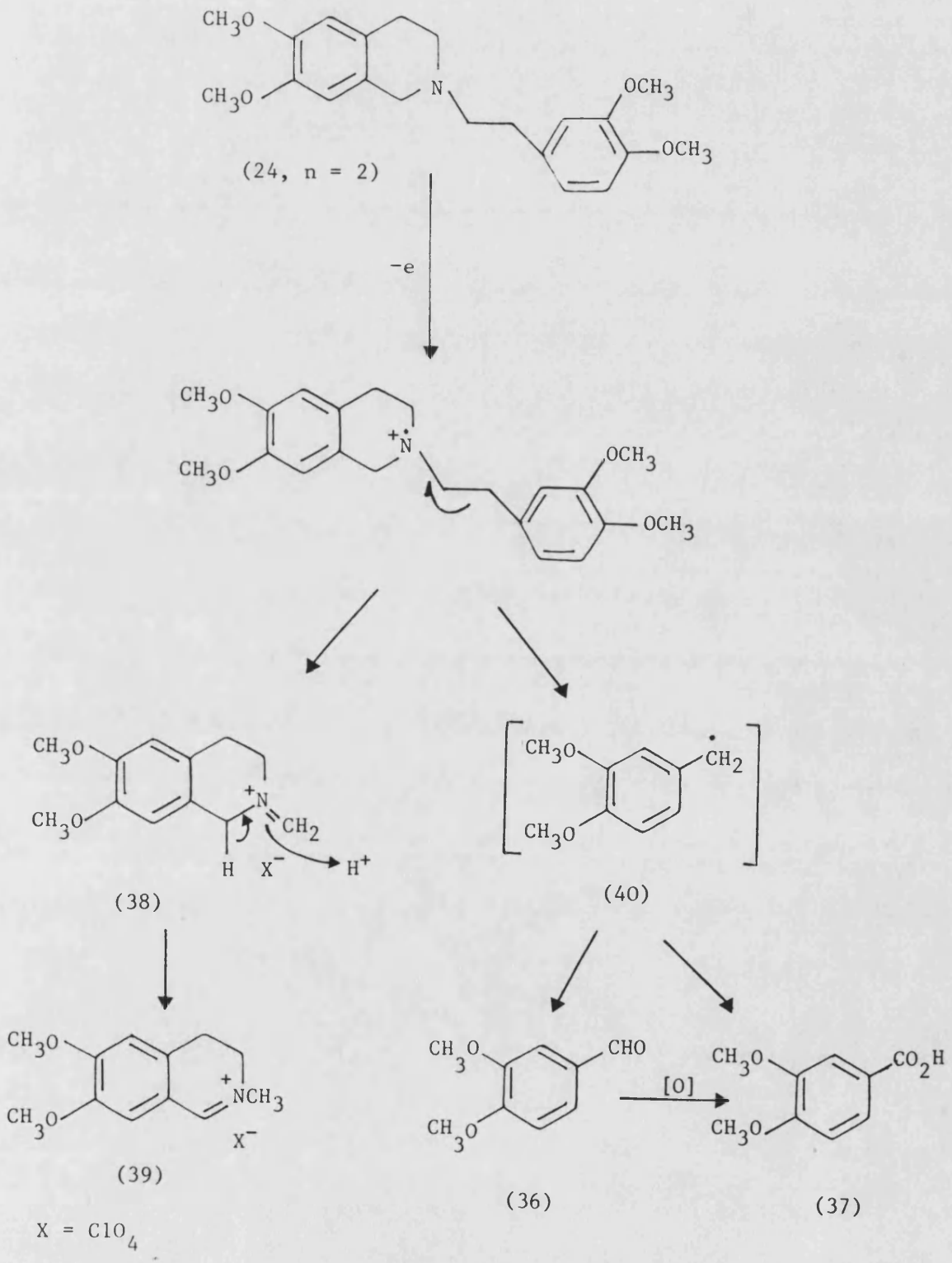
Figure-2. Cyclic voltammogram of N-(3,4-dimethoxyphenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (24 n = 2)



If second, third and fourth sweeps were taken during the voltammetry experiment there was no sign of product peaks, so again we were faced with the probability of a fragmentation of the N-substituent. So it proved in practice and a full scale electrolysis of N-(3,4-dimethoxyphenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (24, n = 2) at an anode potential of +1.1 volts using sodium perchlorate in dry acetonitrile as electrolyte, gave verataldehyde(36), veratric acid (37) and 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium perchlorate (39)[27].

These results lead us to propose the following scheme which indicates that initial ionisation at nitrogen is followed by cleavage of the β-bond (rather than the α-bond as before) of the side chain, this gives a benzyl radical (40) (or its equivalent), which is further oxidised either to veratraldehyde (36) or to the corresponding acid (37), and the iminium salt (38). The latter rearranges to the 3,4-dihydroisoquinolinium salt (39) through a proton shift (see Scheme-2).

Scheme-2

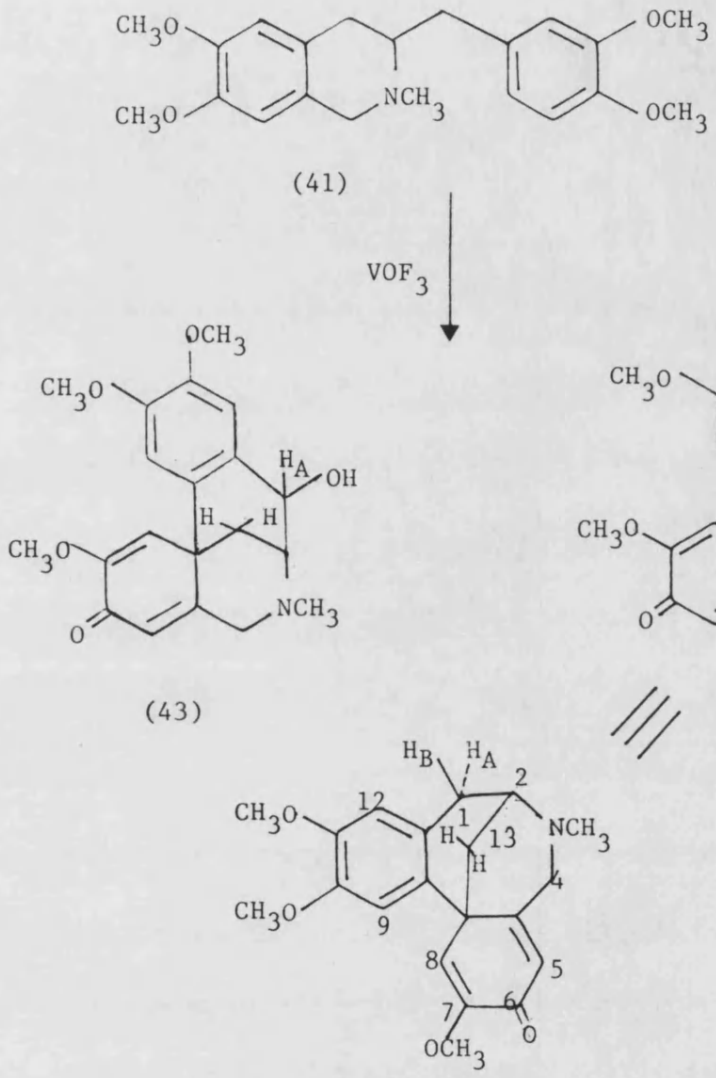

CH3O
CH3O
N
OCH3
OCH3
(24, n = 2)
-e
+N
H
X−
H+
CH2
(38)
(40)
NCH3
(39)
X = ClO4
CHO
[O]
CO2H
(36)
(37)

In both cases oxidation at the nitrogen atom caused fragmentation of the nitrogen-substituent, thus to prevent this, the electrolyses were repeated in acidic conditions in the expectation that now carbon-carbon coupling would be observed in the higher homologue, if not in the lower.

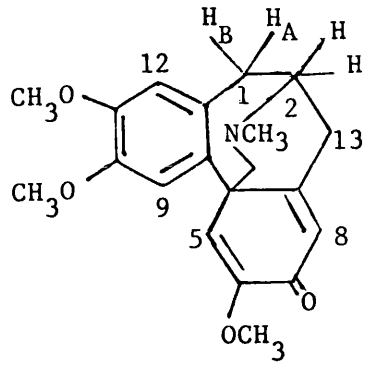
In preparative work, however, both substrates gave complex mixtures and so further studies on them were abandoned.

(iii) The oxidation of 3-aralkyltetrahydroisoquinolines

Following these results we next turned to 3-aralkyl derivatives where cleavage of the substituent is unlikely. There are few references to 3-substituted tetrahydroisoquinolines of this type - testimony to the difficulties involved in their synthesis.[28,29,30]. However, Hartenstein et al[31], have shown that 6,7-dimethoxy-3-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (41) undergoes chemical oxidation with vanadium oxytrifluoride to give the dibenzoazocinone (42) and a small amount of the hydroxy derivative (43). Interestingly, this coupling process proceeds through the formation of a new six-membered ring.

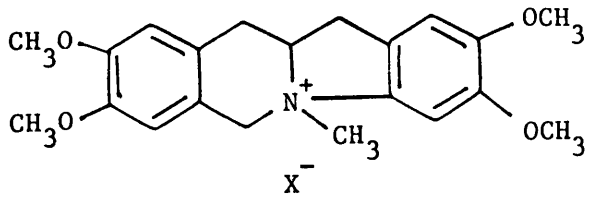


The alternative structure (44), the product of coupling to C-8a of the isoquinoline nucleus, was not found even though its formation would constitute another "allowed" coupling mode.



(44)

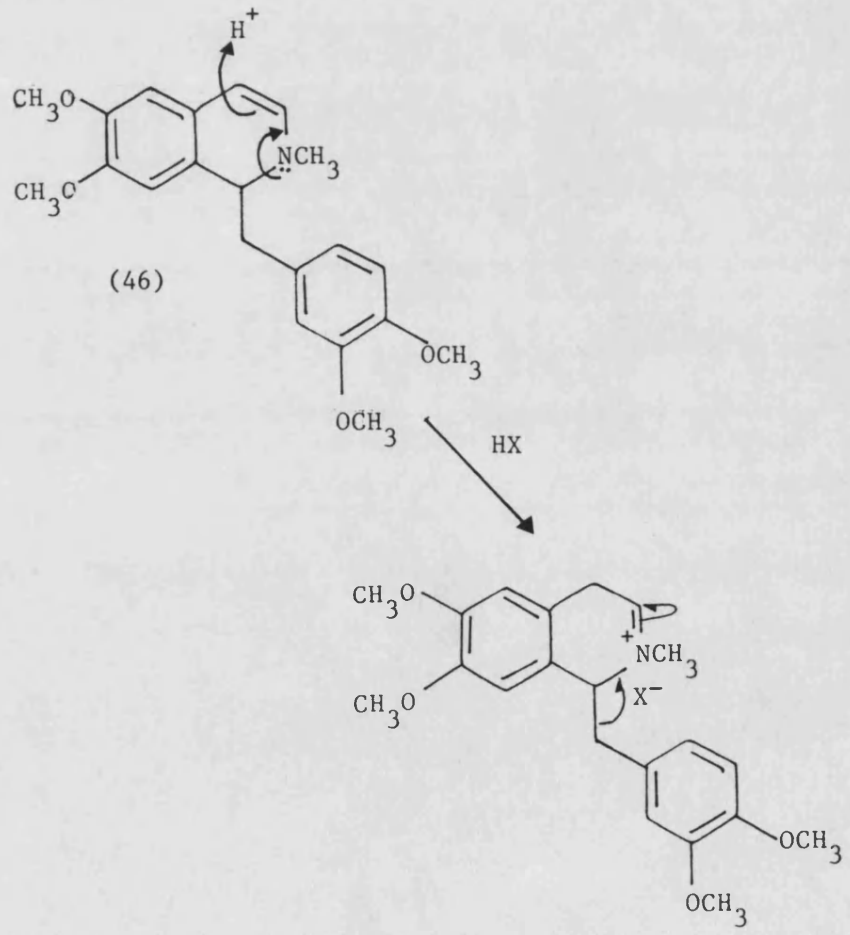
It may be assumed that in a chemical oxidation of this kind the lone pair electrons of the nitrogen atom of the substrate would be complexed by the reagent. Therefore would an electrochemical process on the neutral substrate follow the same path, or would attack take place at the nitrogen atom leading to the salt (45)? This last process would be an example of a 5-endo-trig process and should therefore be disfavoured.



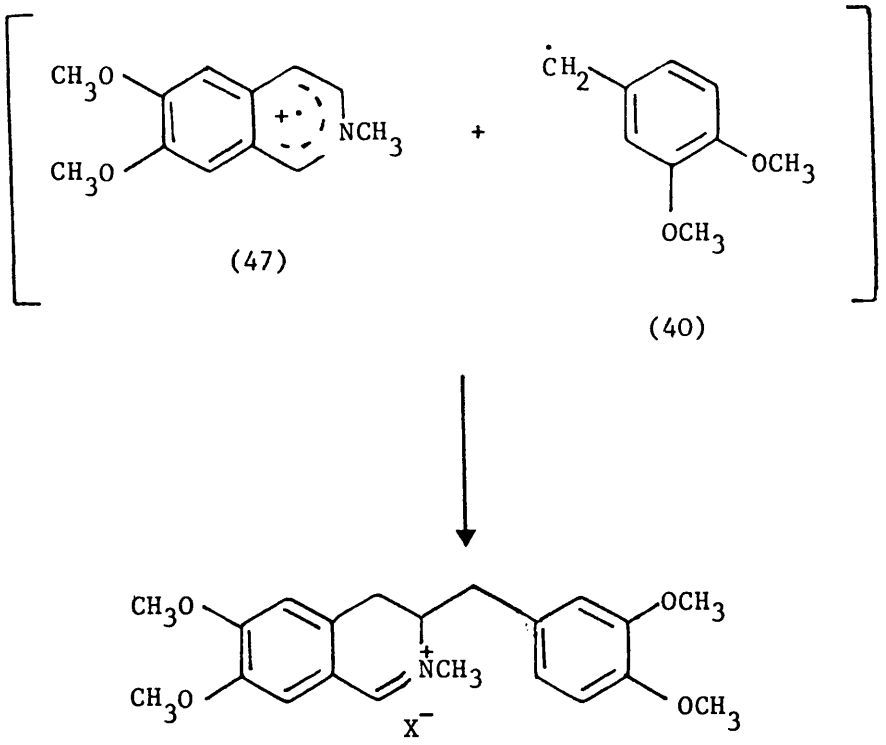
(45)

X = ClO_4

Knabe's[28,29,30] and Sainsbury's groups[32] have previously made the 3,4-dihydro-6,7-dimethoxy-3-(3,4-dimethoxybenzyl)isoquinolinium salt (48) by the rearrangement of the 1-benzyl-1,2-dihydroisoquinoline (46). This is an interesting reaction in which the 1-benzyl substituent cleaves off as a radical and then re-combines with the radical cation (47) within a solvent cage. An intermolecular mechanism of this type is predicted, of course, since the rearrangement constitutes an example of a[1,3]-sigmatropic change and one which may not occur intramolecularly under thermal conditions.



(46)



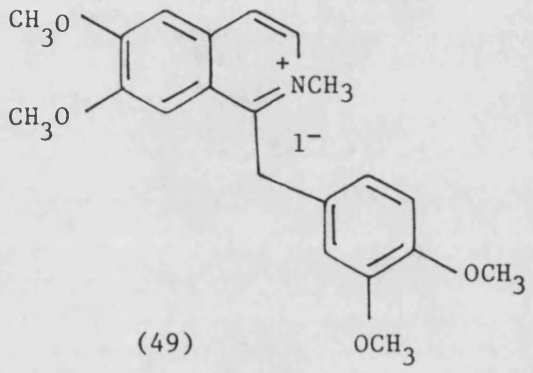
(47) (40)

(48)

X = Cl

Clearly reduction of the salt (48) with sodium borohydride would then yield the starting material (41) for a repetition of Hartenstein's experiment, but now under electrochemical control. Hartenstein did not specify how he prepared compound (41) but presumably followed the same route.

In our hands papaverine methiodide (49) was reduced with lithium aluminium hydride to give the 1,2-dihydro derivative (46). This was treated with 2N hydrochloric acid, the solution was warmed, and sodium borohydride in large excess was then added. Extraction gave the required compound (41).



(49)

LAH

(48) ← HCl — (46)

$NaBH_4$

(41)

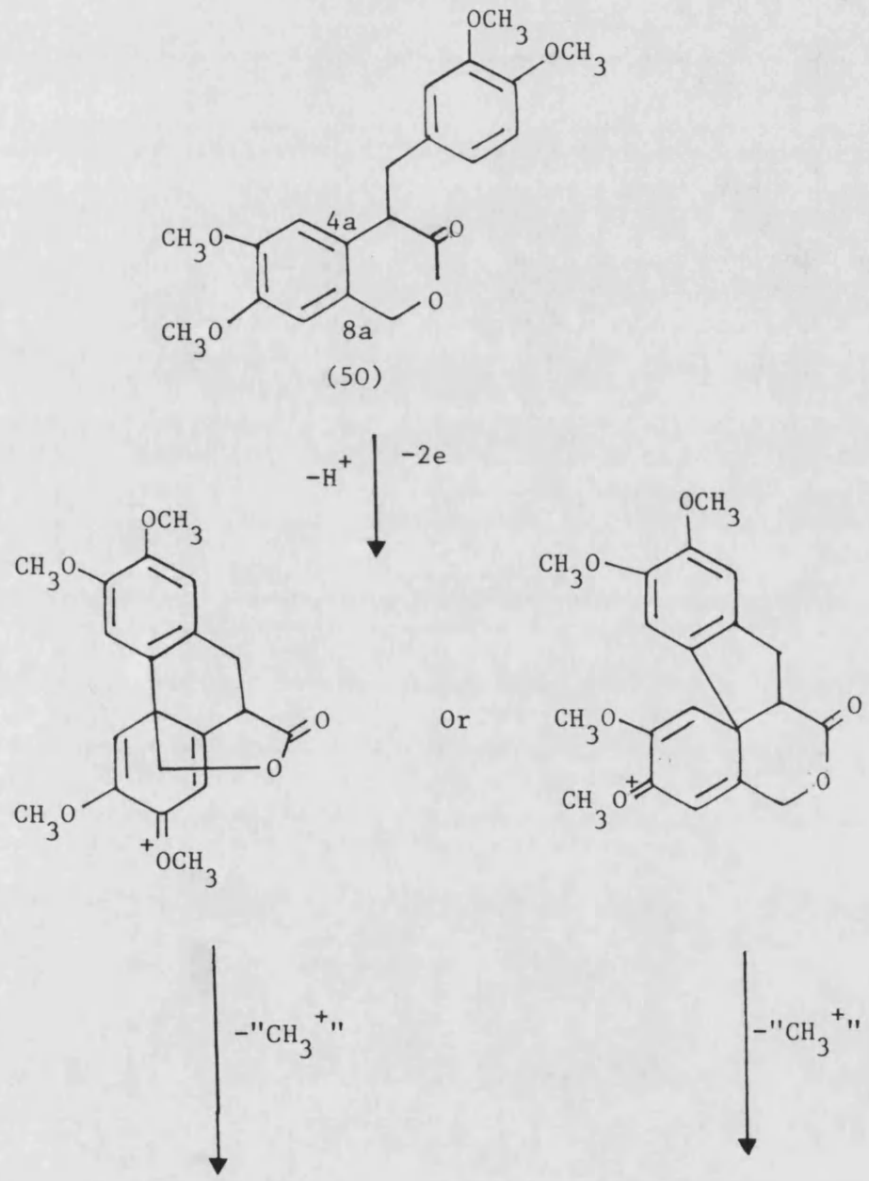
The cyclic voltammogram of this structure shows three waves at potentials similar to those of the 1-benzyltetrahydroisoquinoline (12) and this result may be analysed in an analogous manner, i.e. electron losses from the nitrogen atom and one each from the two benzenoid rings. When it was oxidised at an anode potential of +1.1 volts, none of the salt (45) was isolated from the product, instead the same two tetracycles (42) and (43) previously obtained by the Germans were isolated, in 65% and 5% yields respectively.

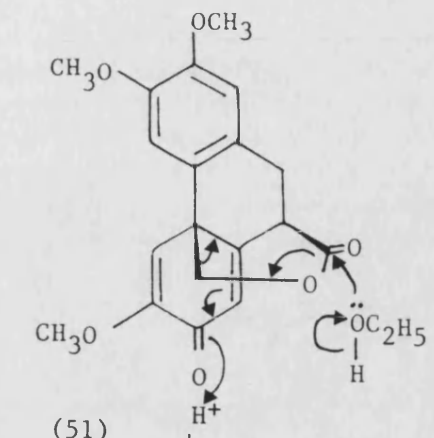
We consider this result to be another piece of evidence to demonstrate the preference for the 6-endo-trig (vs 5-endo-trig) mechanism in aryl-aryl intramolecular coupling reaction of this type.

(iv) The oxidation of 4-benzylisochroman-3-ones

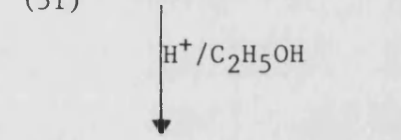
In 1972 Sainsbury and Schinazi reported[33] that the isochroman-3-one (50) when oxidised at an platinum anode gave the phenanthrofurandione (51)[34]. Such a product requires para-para[35] coupling with respect to the 3- and 6-methoxy groups, i.e. via positions 6 and 8a, and its structure was supported[36] by the fact that when it was treated with ethanol and hydrogen chloride, followed by O-methylation of the product, the known tetramethoxydihydrophenanthrene (53) was obtained.

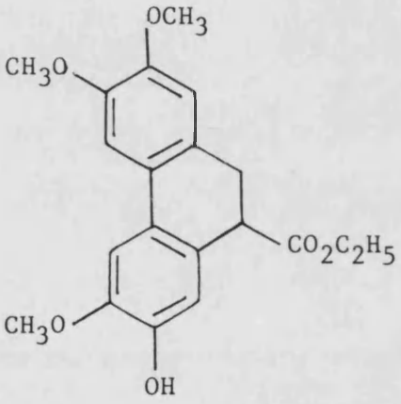
This derivative, which arises through a dienone-phenol[37] rearrangement with concommitant loss of formaldehyde, eliminates the possibility that the alternative structure (54) is the product of the coupling reaction for it would yield the ester (56).



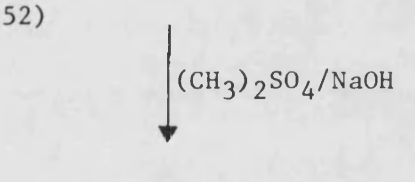


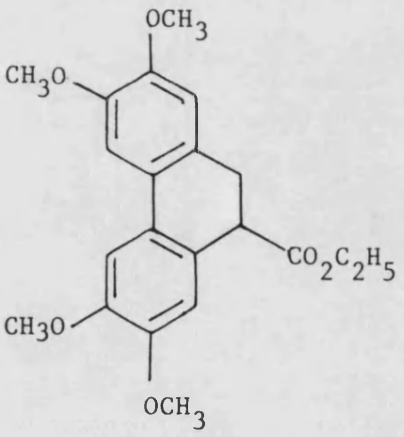
(51)



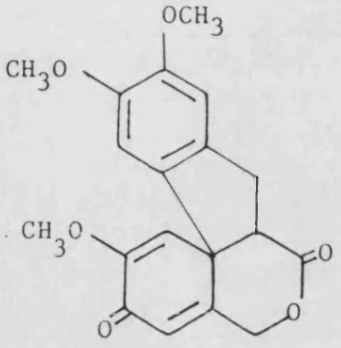


(52)

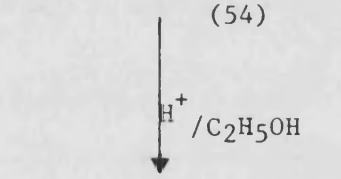


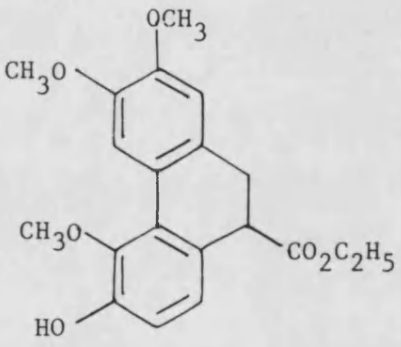


(53)

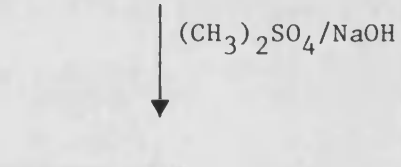


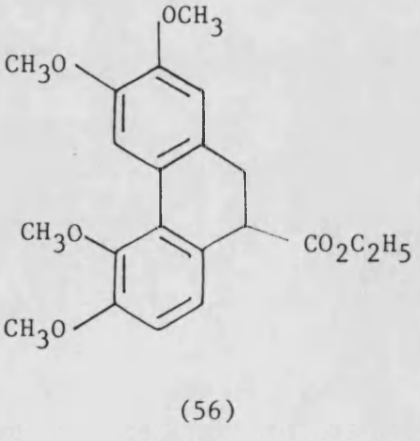
(54)





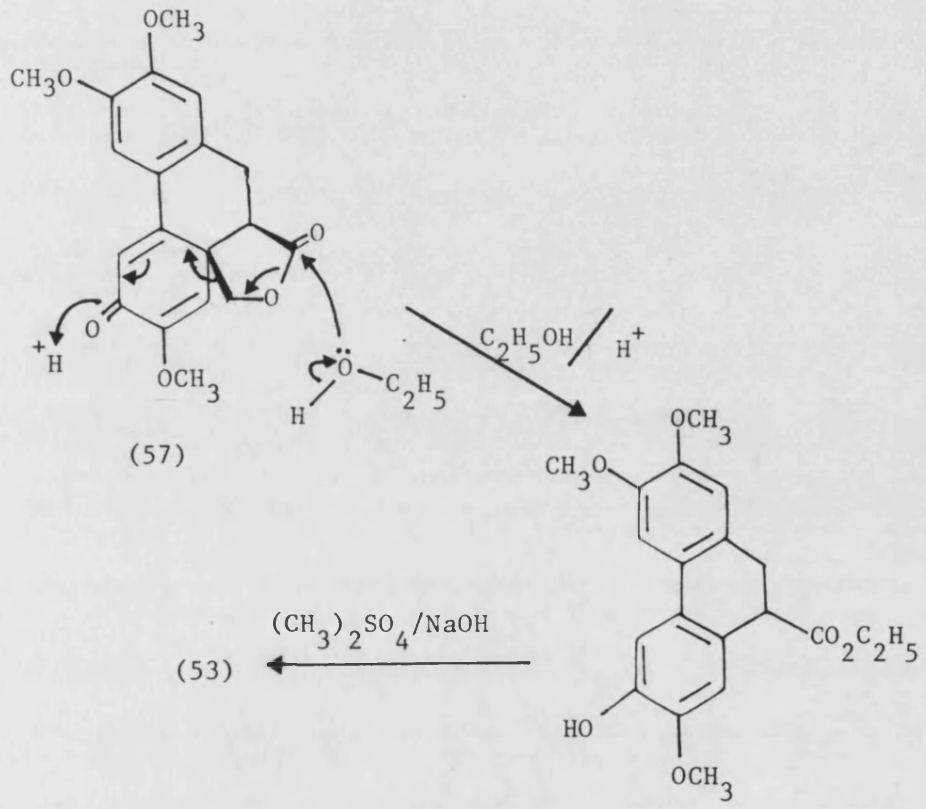
(55)





(56)

Absolute confirmation of the structure of the anodic product was not obtained[38] and the authors realised that a further series of changes emanating from the lactone (57) might also give the same tetramethoxydihydrophenanthrene (53).

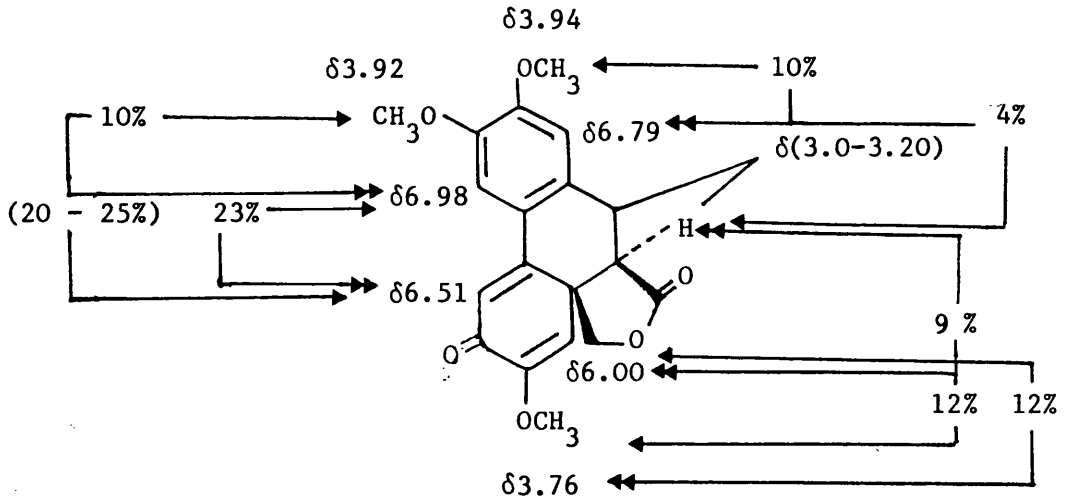


My predecessor Paul Bird[12] set out to synthesise the two trimethoxydihydrophenanthrenes (52) and (55) to settle this anomaly, but this work was halted when access to high field ^{1}H n.m.r. spectroscopy became possible. For example, the evidence from n.O.e enhancement experiments showed clearly that the last possible structure (57) for the coupled product was, most unexpectedly, the correct one.

The ^{1}H n.m.r. spectrum of this last product shows four low field single proton resonances at δ 6.98, 6.79, 6.51 and 6.00. These are assigned to the signals of H-12, H-9, H-1 and H-4 respectively.

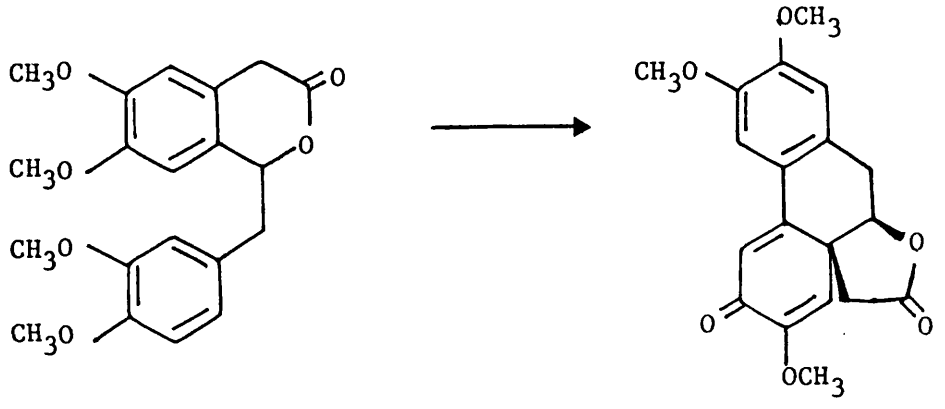
Individual irradiation of the signals at δ 6.51 and δ 6.98 enhance one another (20 - 25%) which immediately rules out structure (51) where the two protons in question are remote from each other. Further studies show that the assignments of the aromatic hydrogen resonances are correct, because

Figure 3. N.O.e experiments relating to the structure of 7a,8-dihydro-3,10,11-trimethoxy-2H-phenanthro[9,8a-b] furan-2,7(5H)dione (57)(→→ indicates position of irradiation.)



irradiation of the methoxy proton signal at δ 3.76 causes a 12% enhancement of the signal at δ 6.00, and vice-versa. The protons of the other two methoxy groups resonate at δ 3.92 and δ 3.94. Irradiation at δ 6.00 also stimulates a 9% increase in the intensity of the methine proton signal (H-7a) adjacent to the lactone carbonyl group, together with the resonances of the H-5α and H-8α protons. The main features of these results are summarized in Figure-3.

Elliot[39] has already shown that the 1-benzylisochromanone (58) affords the γ-lactone (59) when it is oxidised with vanadium oxytrifluoride. Thus, the two sets of results are now in accord: in each case aryl-aryl coupling is followed by rearrangement, but the question still remains why should this rearrangement occur since, for example, structure (51) is very reasonable and does not seem to represent an unstable species?

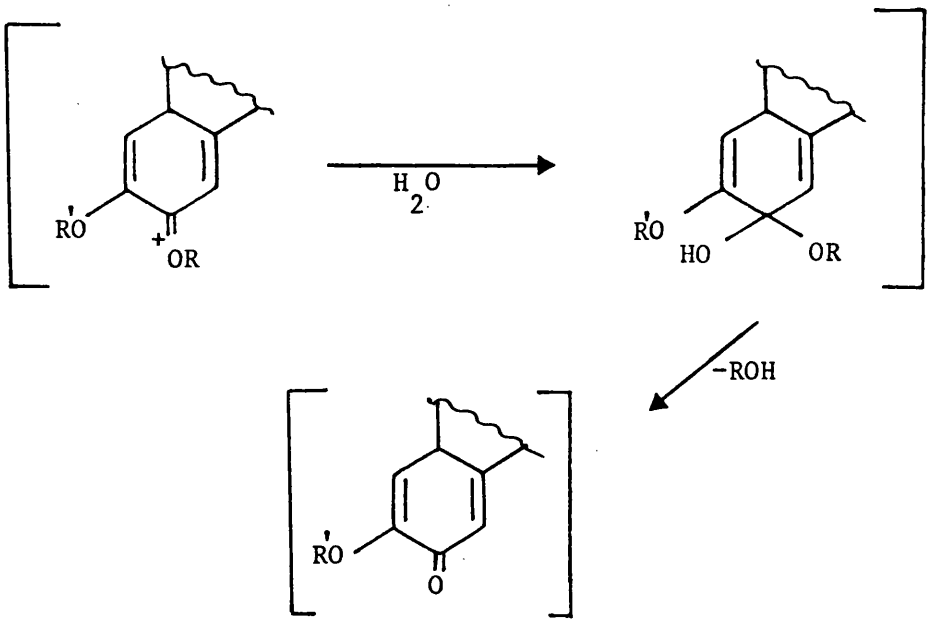


(58) (59)

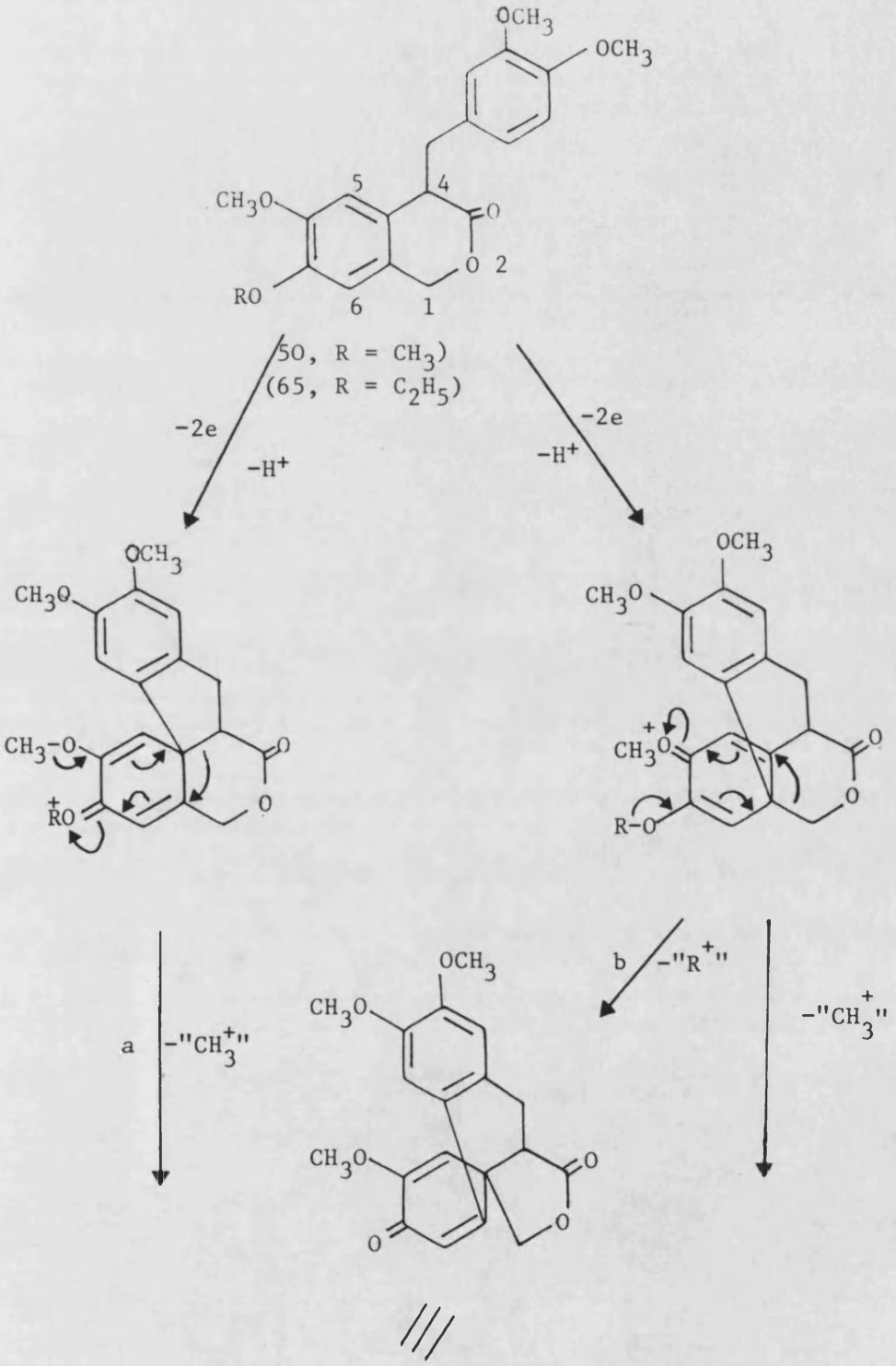
The phenanthrofurandione (57) hereafter referred to as the (γ-lactone) could be formed from the isochromanone in two ways Scheme-3 : (a) by coupling to C-4a, followed by rearrangement and demethylation (route -a) or (b) by coupling to C-8a and migration of the 6-8a bond (route b).

Proof of the coupling mode could be obtained by the oxidation of the ethoxylated isochromanone (65) for via route (a) the ethyl group would be retained, but if route (b) is followed then the ethyl group is lost as shown in Scheme-3.

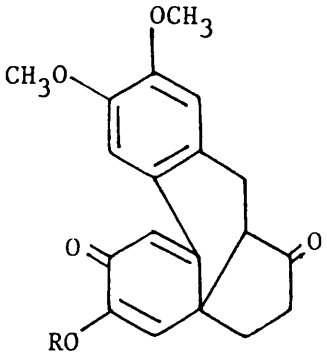
In this scheme it should be noted that for the loss of methyl or ethyl groups the probable mechanism is not simply a cleavage of an alkyl cation but a two step process involving first hydration and then the loss of the appropriate alcohol.

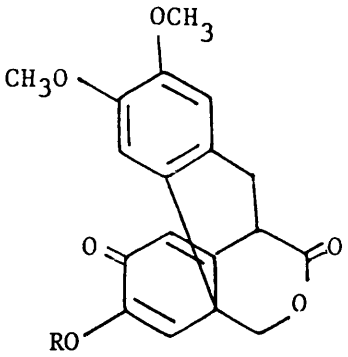


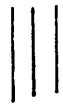
Scheme-3

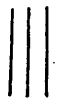

OCH3
OCH3
CH3O
5
4
O
O 2
RO
6
1
50, R = CH3)
(65, R = C2H5)
-2e
-H+
-2e
-H+
OCH3
CH3O
CH3-O
O
O
+
RO
OCH3
CH3O
+
CH3O
O
O
R-O
a
-"CH3+"
OCH3
CH3O
CH3O
O
O
O
b
-"R+"
-"CH3+"

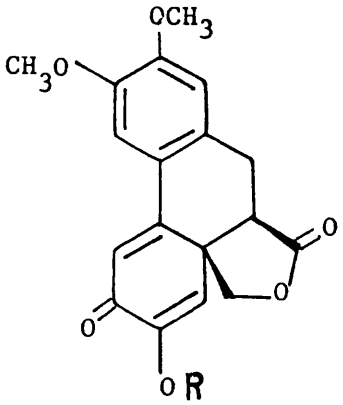
(57)


OCH3
CH3O
O
O
RO

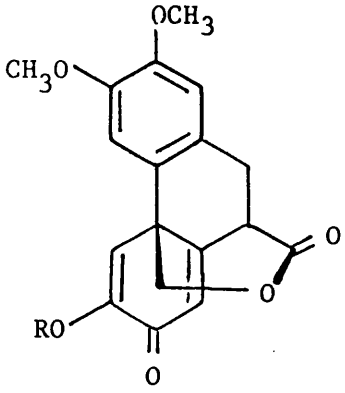

OCH3
CH3O
O
O
O
RO






OCH3
CH3O
O
O
O
O R

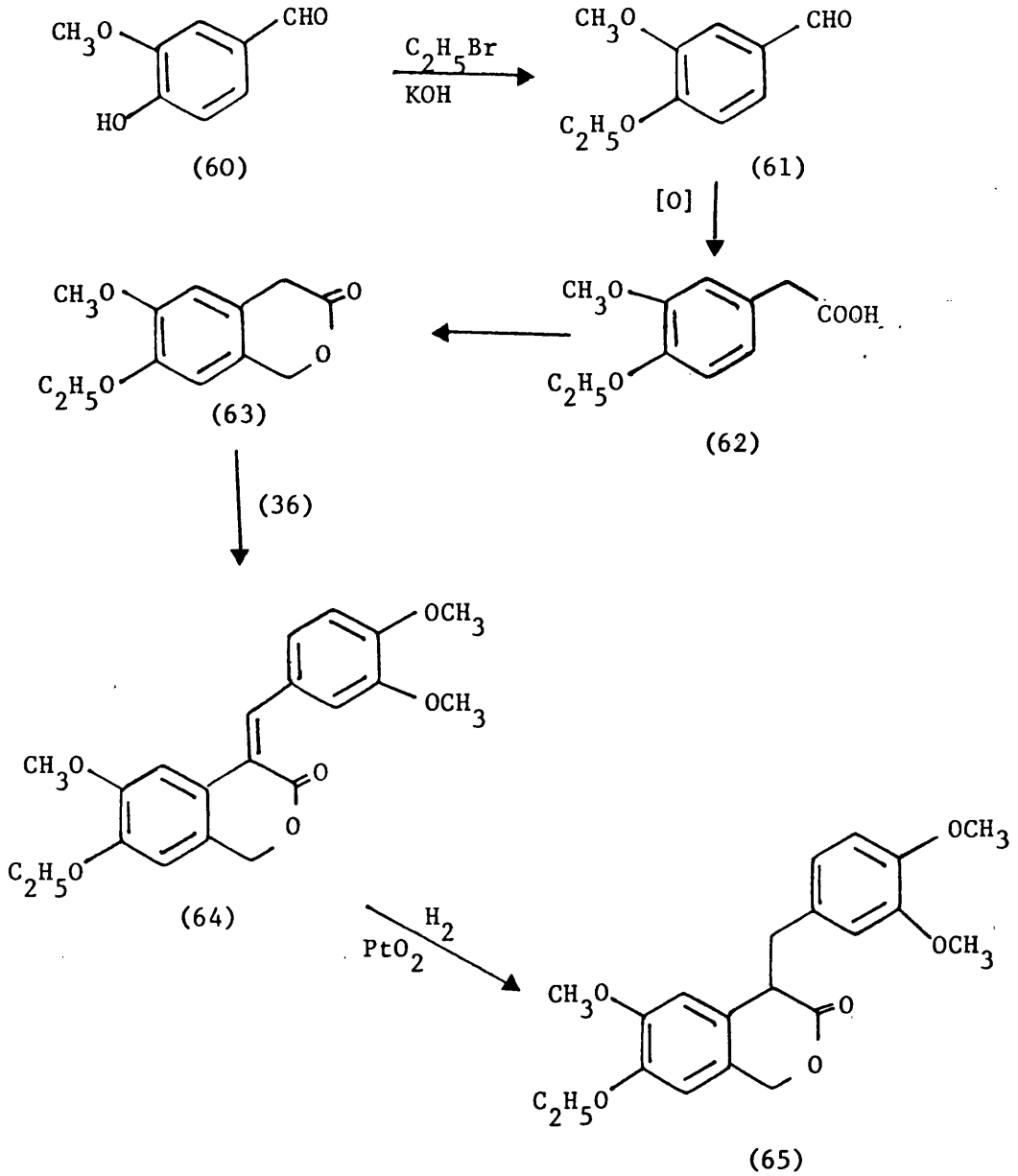
(57)


OCH3
CH3O
O
O
RO
O

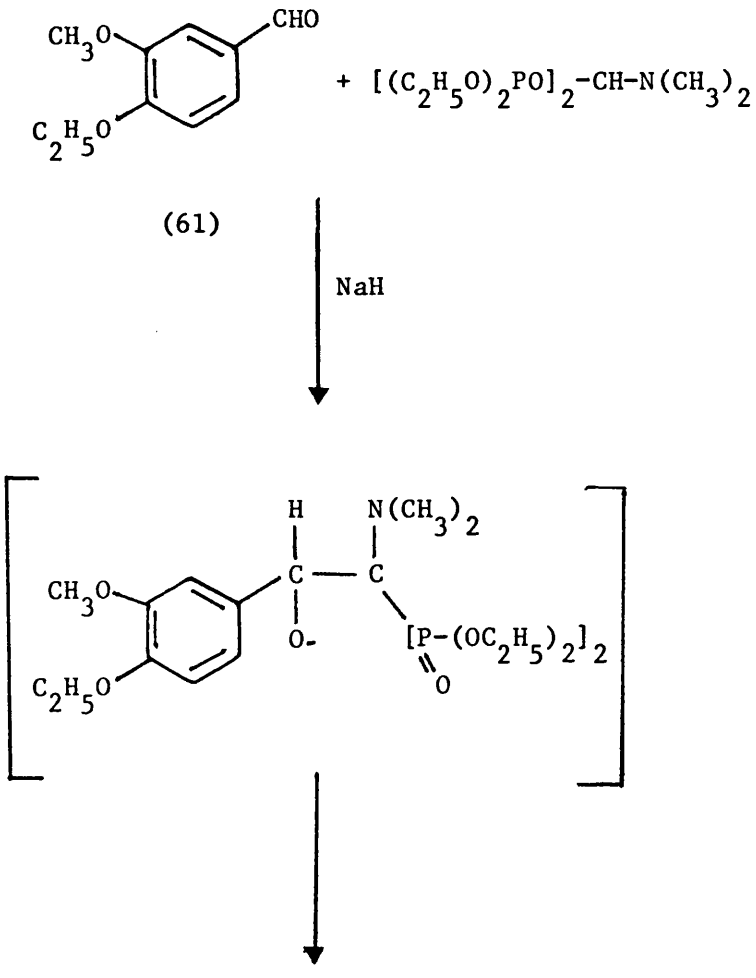
(51)

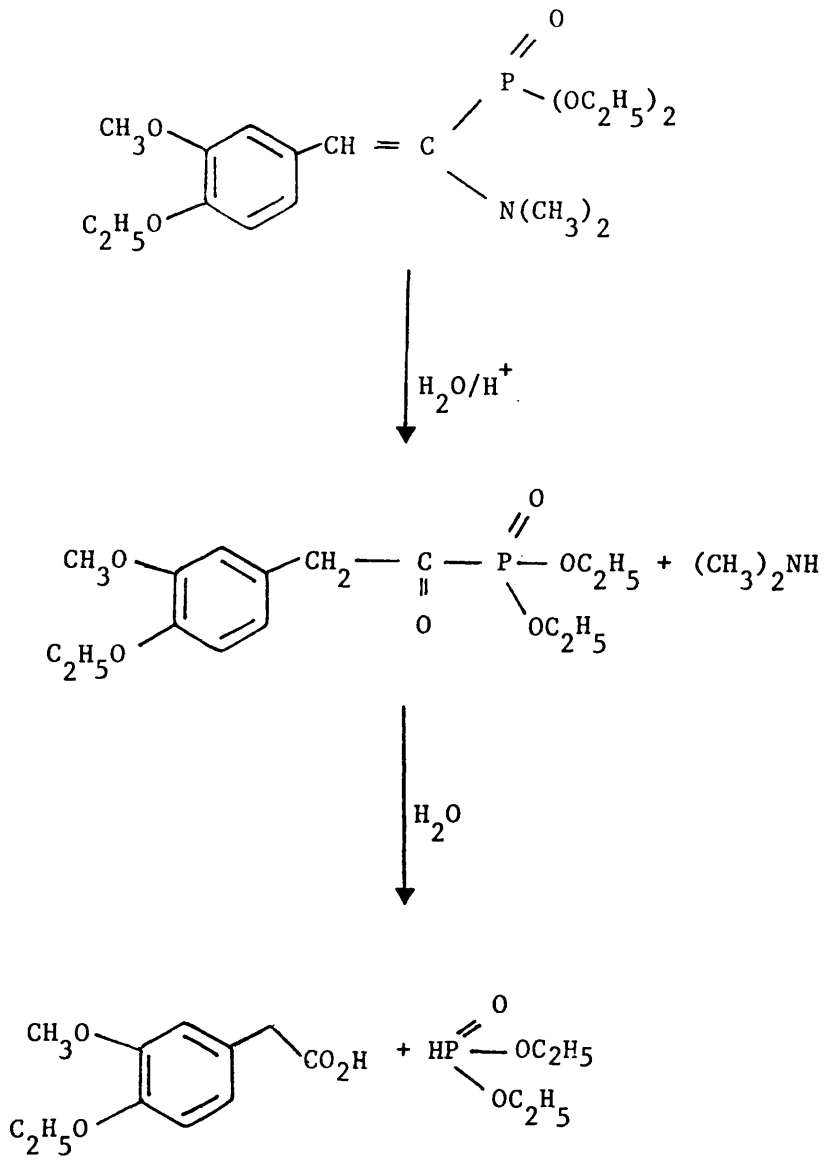
In order to synthesise the substrate for electrolysis, 4-ethoxy-3-methoxyphenylacetic acid (62) is required, and it was at this point the author's work in this programme began. The planned route to the ethoxylated isochromanone is outlined in Scheme 4.

Scheme 4.



4-Hydroxy-3-methoxybenzaldehyde (60) was converted into the O-ethyl derivative (61)[40] by treatment with ethyl bromide and potassium hydroxide solution. In order to "homologate" this aldehyde, several procedures could be used, for example, <u>via</u> the corresponding azlactone[41] (this proved unsuccessful), or from the benzoic acid, by the Arndt-Eistert[42] reaction. However, the most convenient procedure is through a modified Wittig reaction of the aldehyde (61) with tetraethyldimethylaminomethylene diphosphonate (66) in the presence of sodium hydride.[43,44]





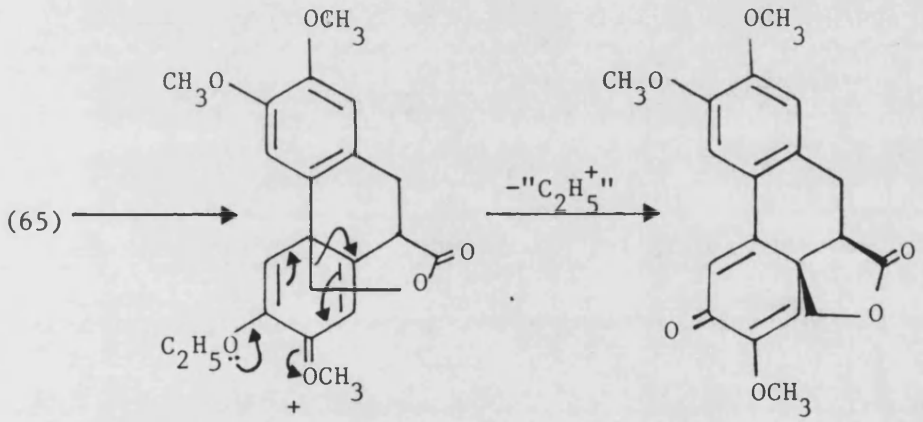
(62)

The required reagent was obtained by reacting dimethylformamide acetal with diethyl phosphite according to the method of Gross and Costisella[45] , followed by deprotonation. Applied to our problem this sequence gave the required acid in 36% yield. Next the acid (62) was cyclised to the isochroman-3-one (63) by reaction with formaldehyde and hydrochloric acid and when reacted with verataldehyde(36) in the presence of pyrrolidine This compound afforded the benzylidene derivative (64) as a mixture of (E)- and (Z)-isomers. Finally reduction of the mixed isomers to the required substrate (65) was effected by hydrogenation over platinum oxide.

The cyclic voltammogram of the labelled isochromanone shows a broad wave at ≃ +1.1v corresponding to the loss of an electron from either of the two benzenoid π-systems and an electrolysis of it was carried out at this voltage using an H-type cell. The anode compartment being charged with the substrate in acetonitrile containing sodium perchlorate as the supporting electrolyte. The electrodes were made of platinum gauze and after the passage of 2F mol^{-1} of current the anolyte was collected and worked up to yield the same γ-lactone (57) as obtained by anodic oxidation of the tetramethoxylated isochromanone (50).

The yield of the purified γ-lactone (57) was 67%, but no evidence for the presence of the ethoxylated analogue was obtained, the mass-loss being made up from over-oxidation products such as verataric acid.

This the major (probably the only) coupling mode occurs through route (b), meaning that initial coupling occurs via a six-membered ring forming reaction to C-8a, followed by a rearrangement mediated by the participation of the lone pair electrons of the C-7 ethoxyl group:

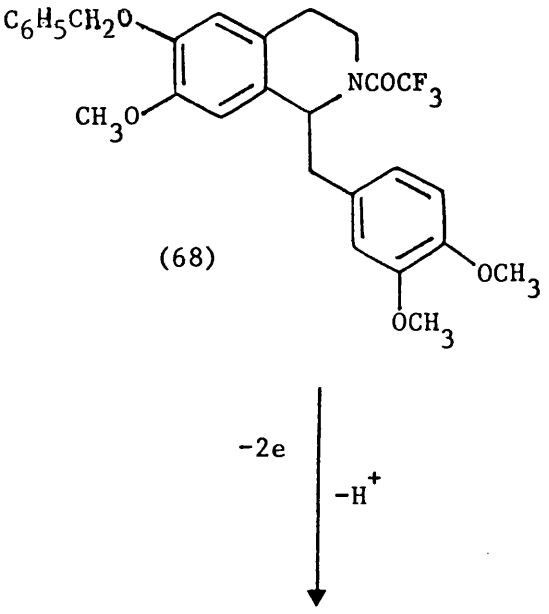


(67) (57)

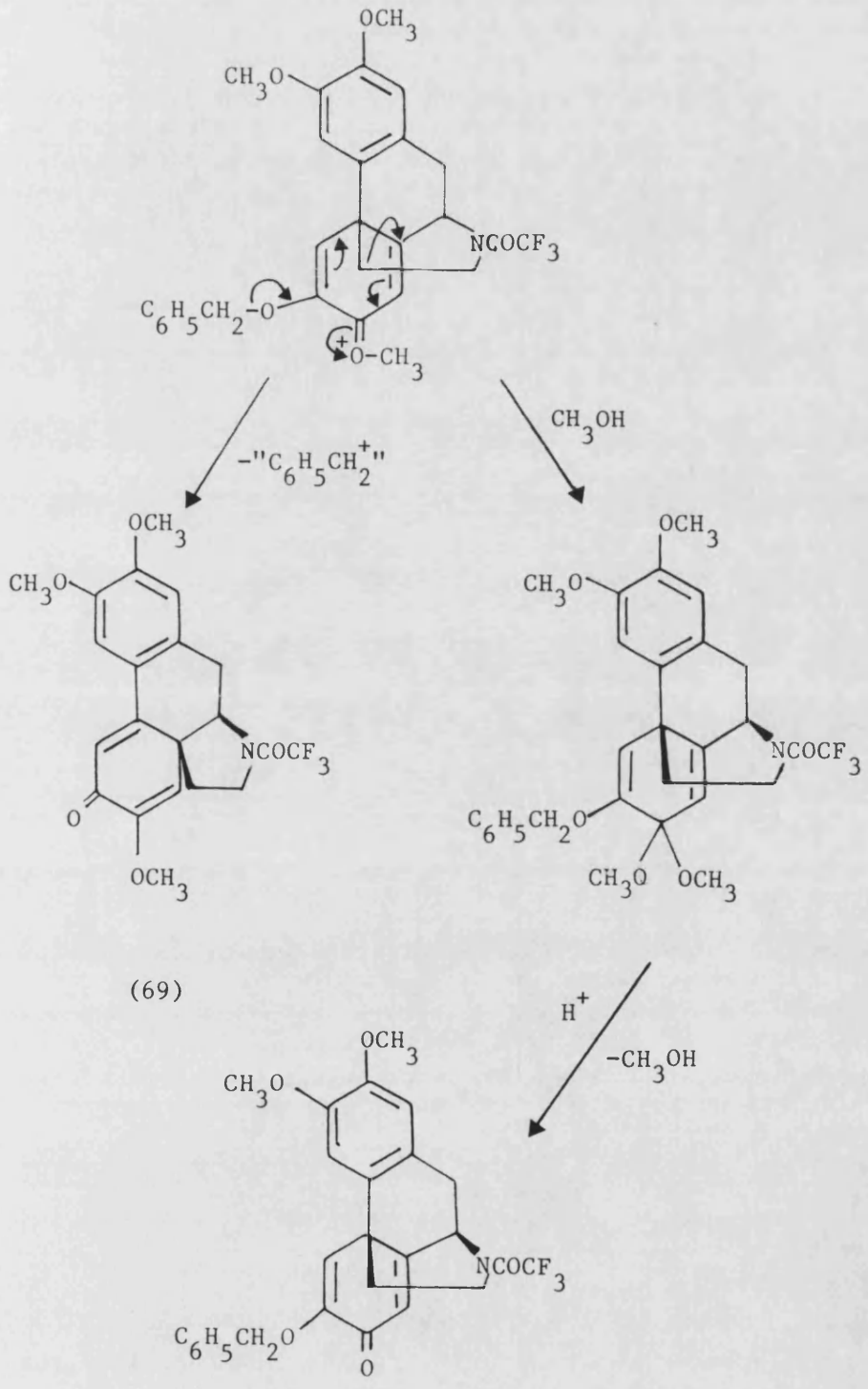
This is further proof of the preference for <u>6-endo-trig</u> coupling reactions at the anode, but it is curious that having reacted the point of the δ-lactone cation (67) this sequence does not end there with loss of the methyl cation or its equivalent.

Schäfer[46] and his colleagues have shown recently that a similar rearrangement occurs during the coupling of the 1-benzyltetrahydroisoquinoline (68). This leads to both the morphinandienone (70) and the neospirodienone (69). However, should methanol be added to the electrolysis medium formation of the latter product is repressed, presumably because methanol assists the loss of the methyl substituent, possibly as shown in Scheme 5.

Scheme 5.

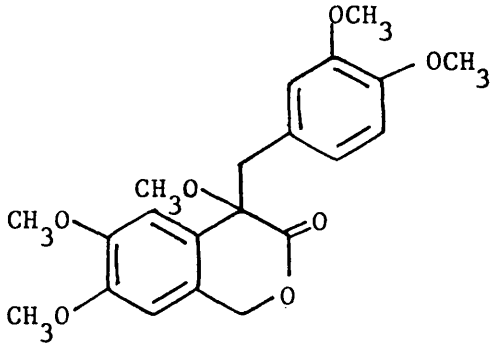


(68)

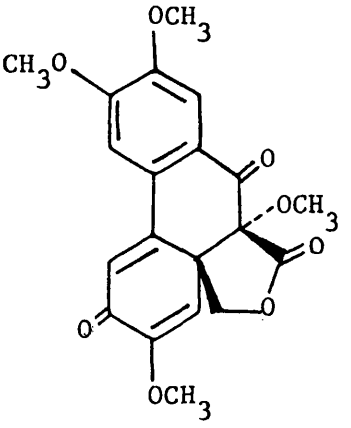

OCH3
CH3O
NCOCF3
C6H5CH2O
O-CH3
-"C6H5CH2+"
CH3OH
OCH3
CH3O
NCOCF3
O
OCH3
OCH3
CH3O
NCOCF3
C6H5CH2O
CH3O
OCH3
(69)
H+
-CH3OH
OCH3
CH3O
NCOCF3
C6H5CH2O
O

(70)

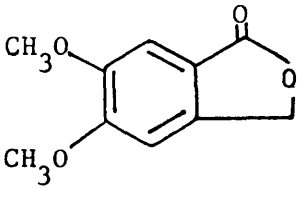
We then set out to examine the effect of adding methanol to the electrolysis medium of our tetramethoxylated isochromanone (50). The results were very different to those of Schäfer, for example, the major product was the pentamethoxylated isochromanone (71), together with the some of the γ-lactone (57) and its methoxylated derivative (72). In addition veratraldehyde (36), veratric acid (37) and the isobenzofuranone (73)[47,48] were obtained. The proportions of this mixture varied depending upon whether water was mixed with the methanol or not. If present then the amounts of the fragmentation products were increased over those of the coupled products.



(71)

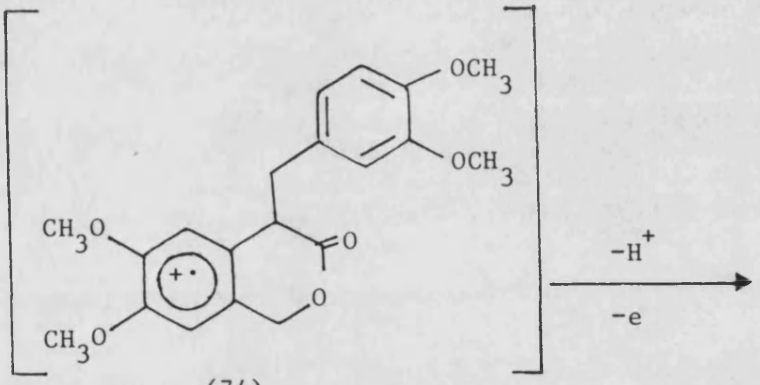


(72)

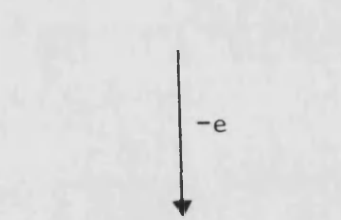


(73)

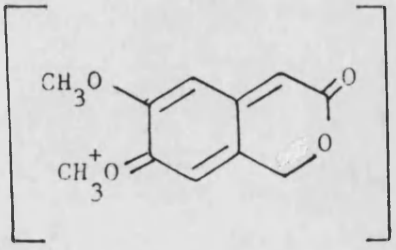
It seems that the formation of all these products can be explained if it is assumed that aryl-aryl coupling[4,1] is in competition with deprotonation and capture of a nucleophile (e.g. water or methanol). Thus the radical cation (74) or its equivalent, may either couple to yield the γ-lactone (57) or deprotonate to the cation (75), which may then capture methanol to afford the pentamethoxylated isochromanone (71), or cleave to yield the benzylic cation (77) which, particularly in the presence of water, leads on to veratraldehyde (36) and veratric acid (37).



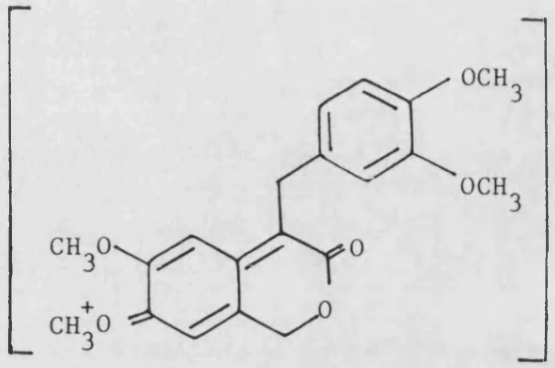
(74)



(57)

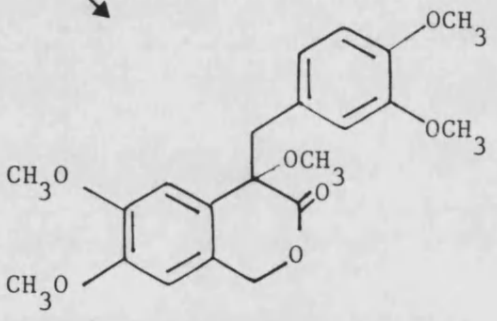


(76)

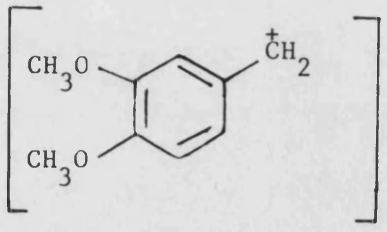


(75)

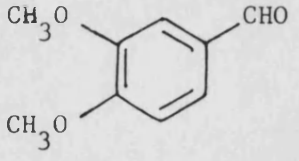
CH_3OH



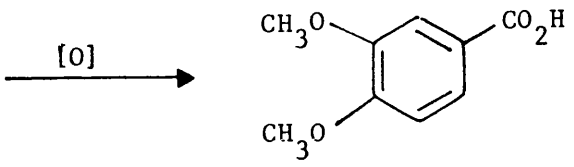
(71)



(77)

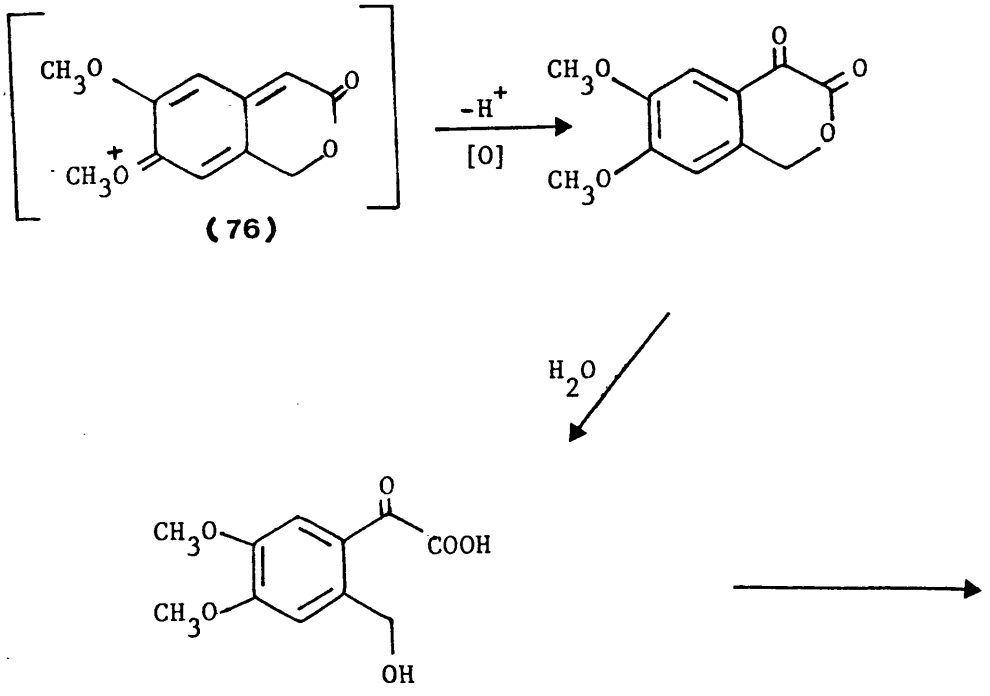


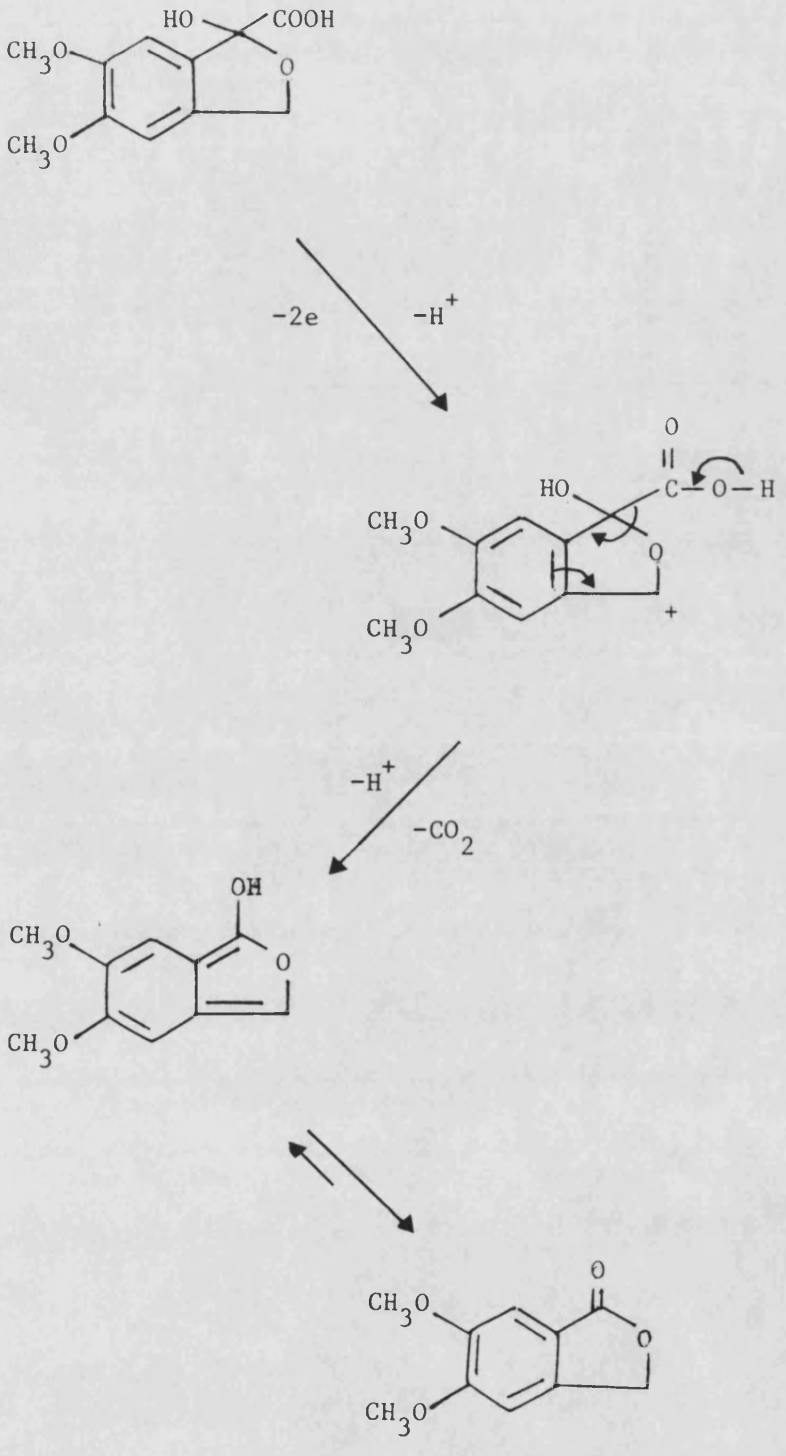
(36)



(37)

The other product of the latter cleavage process, the cation (76) may also capture water and undergo further oxidation to give the benzisofuranone (73), perhaps as shown below:



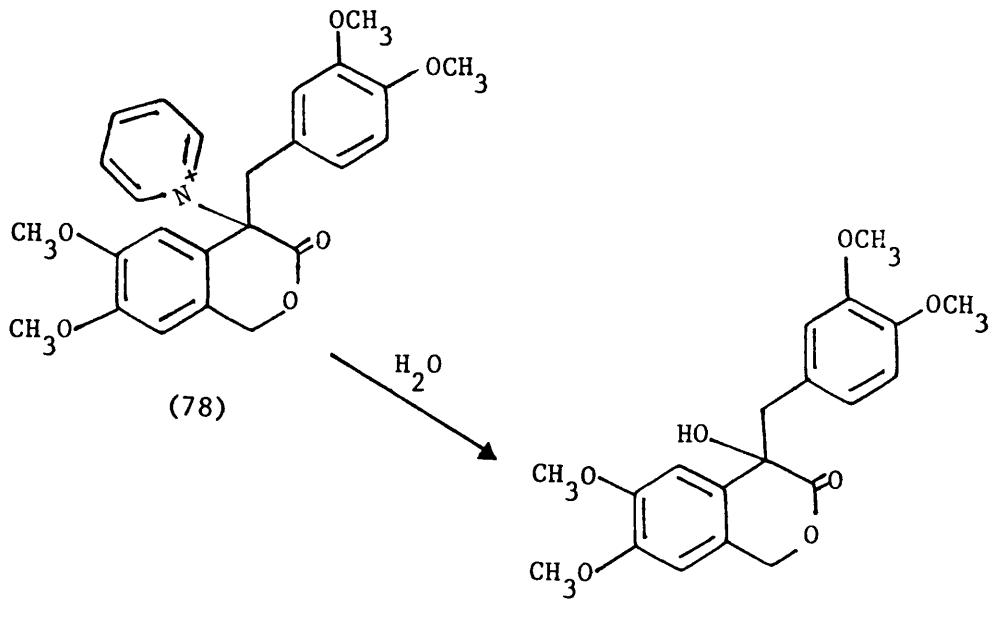

HO
COOH
CH_3O
O
CH_3O
-2e
$-H^+$
O
C
O
H
HO
CH_3O
O
CH_3O
+
$-H^+$
$-CO_2$
OH
CH_3O
O
CH_3O
O
CH_3O
O
CH_3O

(73)

Circumstantial evidence in support of this scheme is provided by the fact that if 6,7-dimethoxyisochroman-3-one is oxidised anodically, the same benzoisofuranone (73) is produced in good yield.

As confirmation of structure an authentic sample of the lactone (73) was prepared by a literature route[47] from the chloroformylation of 3,4-dimethoxybenzoic acid (37).

A difference between the 4-benzylisochromanone (50) and 1-benzyltetrahydroisoquinoline (68) is the "acidity" of the proton at C-4 in the isochromanones which allow the deprotonation type of reaction to occur so easily. We have subsequently shown that other nucleophiles, such as pyridine, will form derivatives with isochromanones during anodic oxidation. For example, the 4-benzylisochromanone (50) yields the salt (78) which, after aqueous work up leads to the alcohol (79).

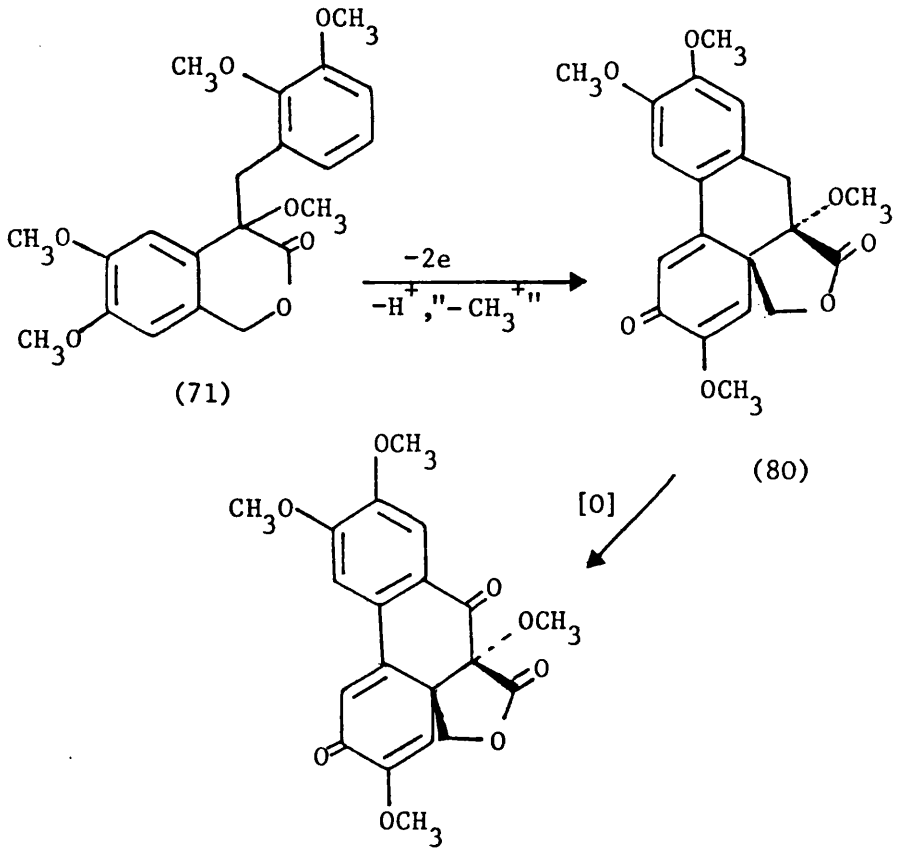


(78)

(79)

The same hydroxylated product (79) is formed if water alone is added to the electrolyte prior to electrolysis. A further point concerns the origin of the methoxylated γ-lactone (72). Is it formed by oxidation of the pentamethoxylated (71), or is it a product of methoxylation of the γ-lactone (50) itself?

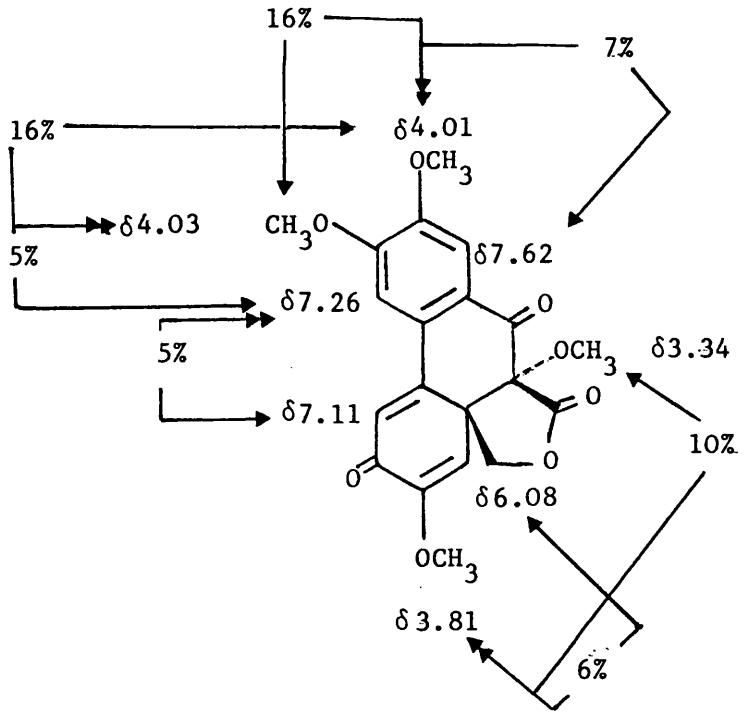
We cannot be totally certain, but we can show that anodic oxidation of the pentamethoxylated isochromanone (71) does lead to the methoxylated γ-lactone (72). Interestingly, none of the dione (80) was isolated, although we assume it to be an intermediate in the reaction (it is clearly very easily oxidised at the anode potential used, +1.1 volts!).



The relative stereochemistry of this final structure (72) was deduced by n.O.e enhancement studies conducted by my colleague Stephen Hall (undergraduate project, 1984).[49] The results are summarized in the following diagram, (Figure 4).

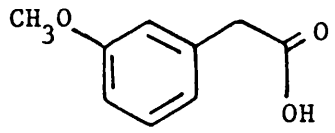
Figure 4. Summary of n.O.e. experiments on the trione (72)

→→ indicates point of irradiation.

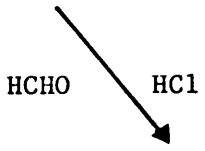


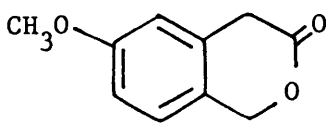
We next tried the addition of a series of other latent nucleophiles in attempts to intercept the rearrangement process, but to no avail (it should be remembered that many potentially suitable reagents for this purpose are ruled out because they are readily oxidised under the conditions of our experiment).

Another way of arresting the rearrangement would be to examine the anodic behaviour of an isochromanone lacking a C-7 alkoxyl group, so we next prepared the dimethoxylated structure (84) from 3-methoxyphenylacetic acid (81) and 3-anisaldehyde by the usual route:

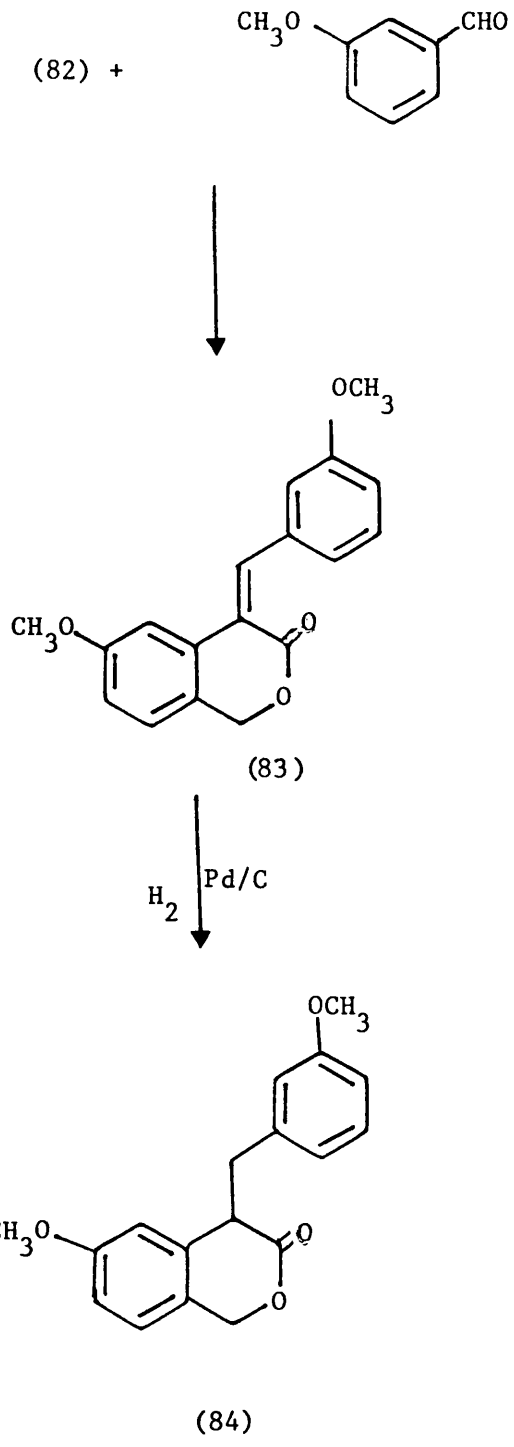


(81)



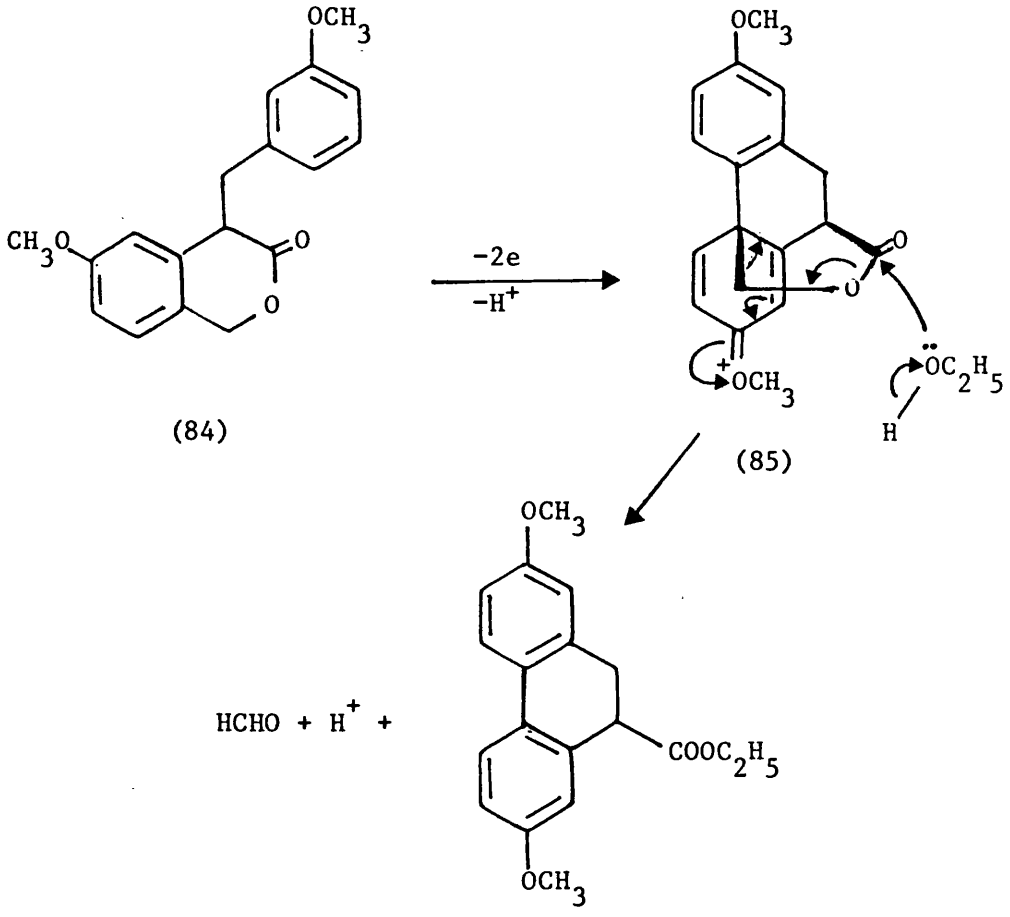


(82)



(84)

To our surprise when the compound was oxidised the only product we were able to isolate was the dihydrophenanthrene ester (86). On reflection the origin of the ethyl group is readily explained since commercial chloroform (containing ethanol as a stabilizer) was used during extraction of the anolyte, and we are forced to conclude that the cation (85), or its equivalent, is indeed generated. This remains until the end of the electrolysis when chloroform/ethanol is added. Nucleophilic attack by the solvent impurity then allows the formation of the dihydrophenanthrene ester (86).

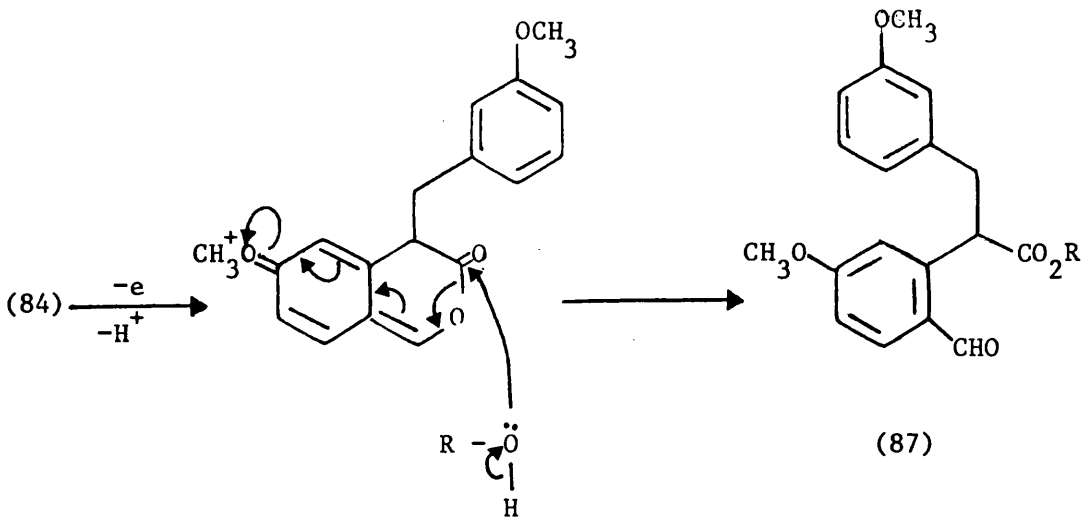


(84)

(85)

(86)

If ethanol is removed from the solvent, a complex mixture of products formed, but if other latent nucleophiles (alcohols) are deliberately added prior to electrolysis a competitive process occurs, namely nucleophilic ring-scission of the isochromanone ring, affording aldehydic esters (87). This suggests that contrary to usual concepts, intramolecular cyclisation is slower than intermolecular attack by an independent nucleophile.

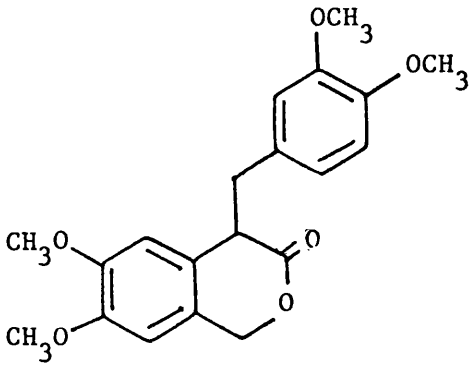


R = CH_3

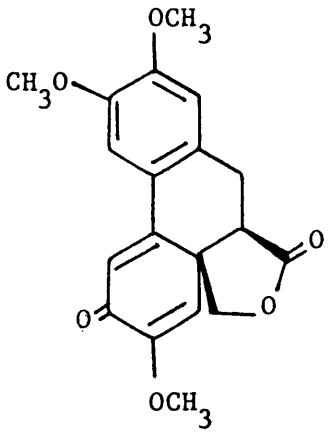
These results indicated to us that perhaps isochromanones are not suitable substrates for conversion into δ-lactones(51) and this study was brought to a close.

(v) The preparation and oxidation of 4-benzylisoquinolin-3-ones

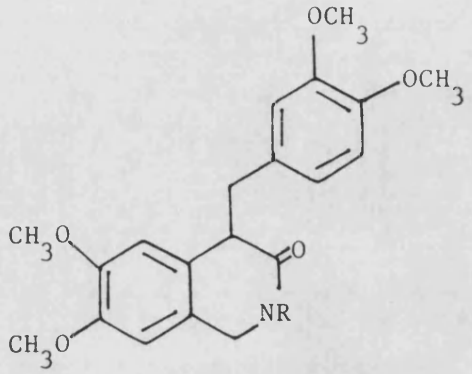
Indeed although the coupling reactions of isochromanones (e.g. 50) are intellectually interesting, the ultimate products (e.g. 57) have no pharmacological value. On the other hand, analogous structures (89, X = O)and (90) containing a nitrogen atom derivable from the lactams (88) are much more likely to show biological activity especially if in subsequent chemistry these compounds could be reduced to amino derivatives. Structure (89 X = O) would then, for example, give rise to a series of isomorphinan (89, X = H_2) bases.



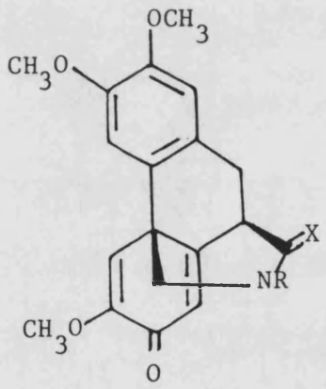
(50)



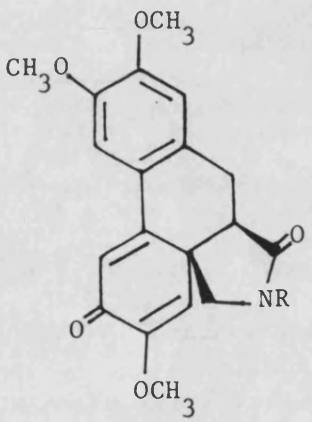
(57)



(88, R = CH_3)



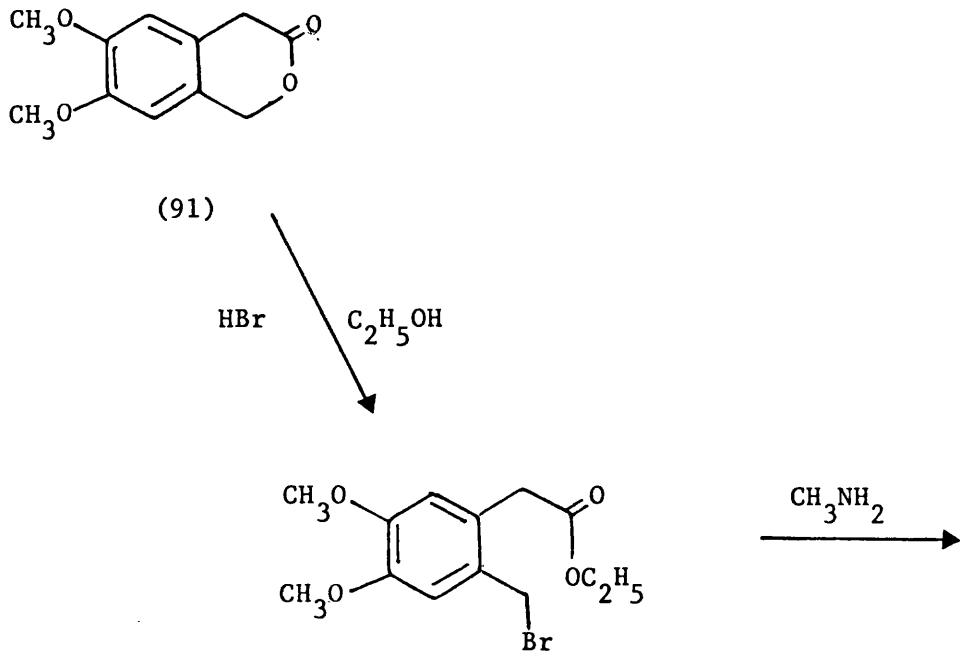
(89)

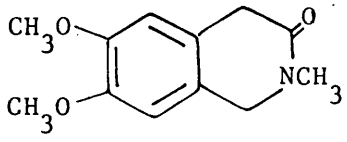


(90)

X = (O, H_2)

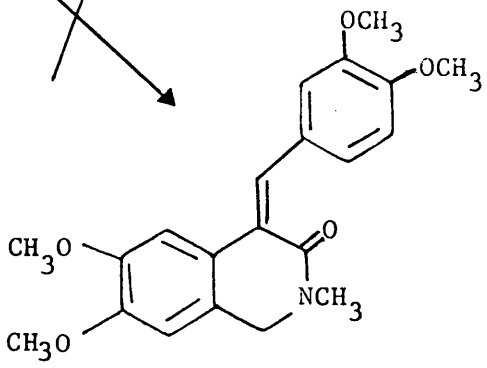
Before such work could be contemplated, however, it was necessary to make the isoquinolinones (88) and study their electrochemical behaviour. This is not straight forward as the parent isoquinolinone (92), made by the method of Brossi and Finkelstein,[50,51] does not react with veratraldehyde to give the corresponding benzylidene derivative (93) in the same way that the simple isochromanone (91) yields the benzylidene isochromanone (109). Direct alkylation also fails with 3,4-dimethoxybenzyl bromide (94) and base largely because the anion of the isoquinolinone promotes the formation of triveratrylene (95)[52] and tetraveratrylene (96).





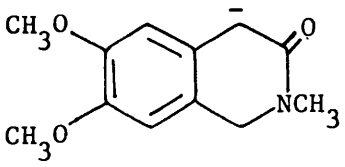
(92)

(36)



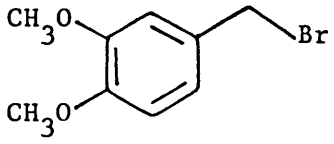
(93)

B

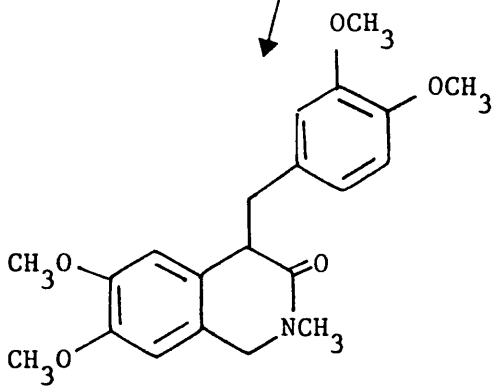


BH^+

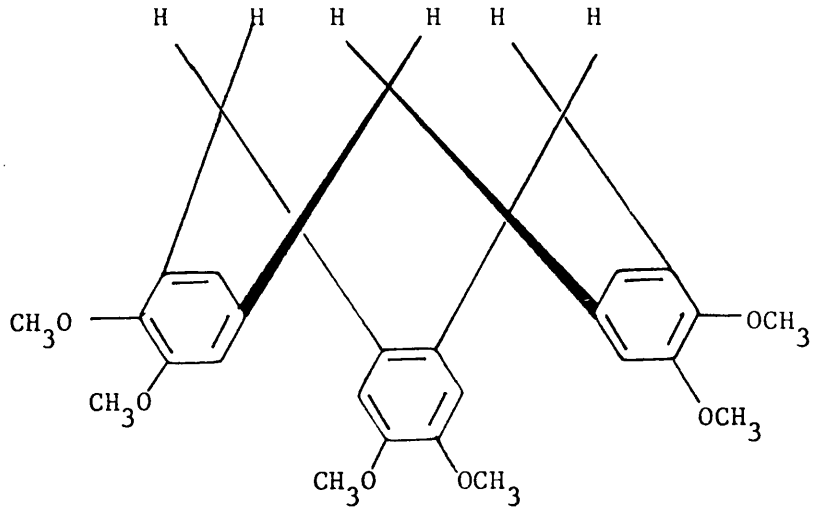
+



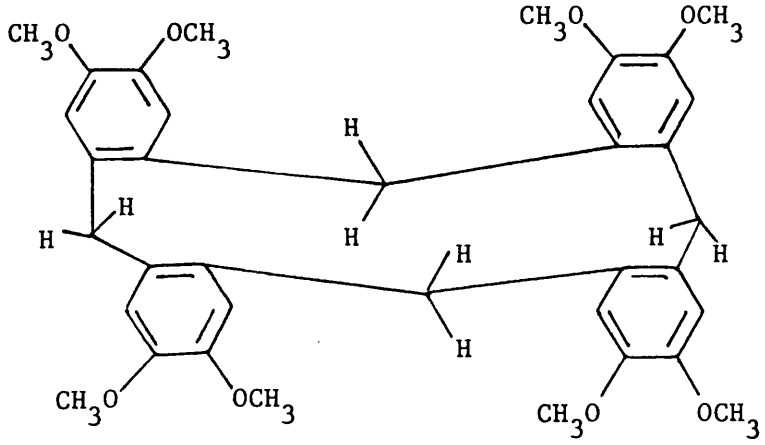
(94)



(88)

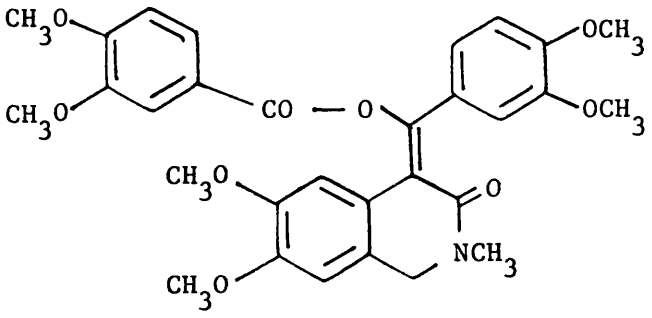


(95)



(86)

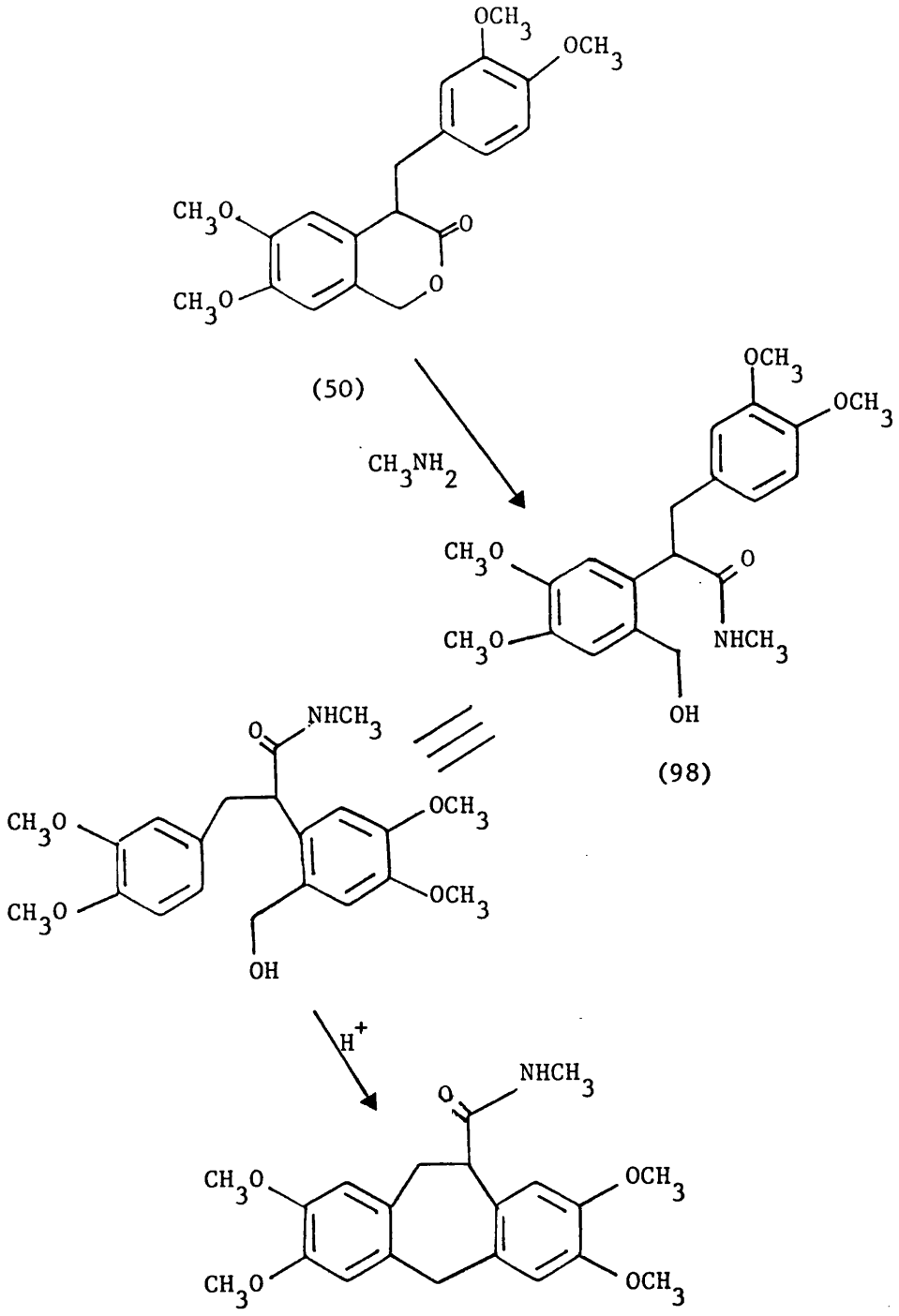
When the lactam (92) was treated with the much more reactive veratroyl chloride , however, the reaction proceeds too far and now the C,O-diacylated product (97) is obtained. Attempts to remove the O-acyl group by hydrolysis resulted in removal of the entire C-4 substituent.



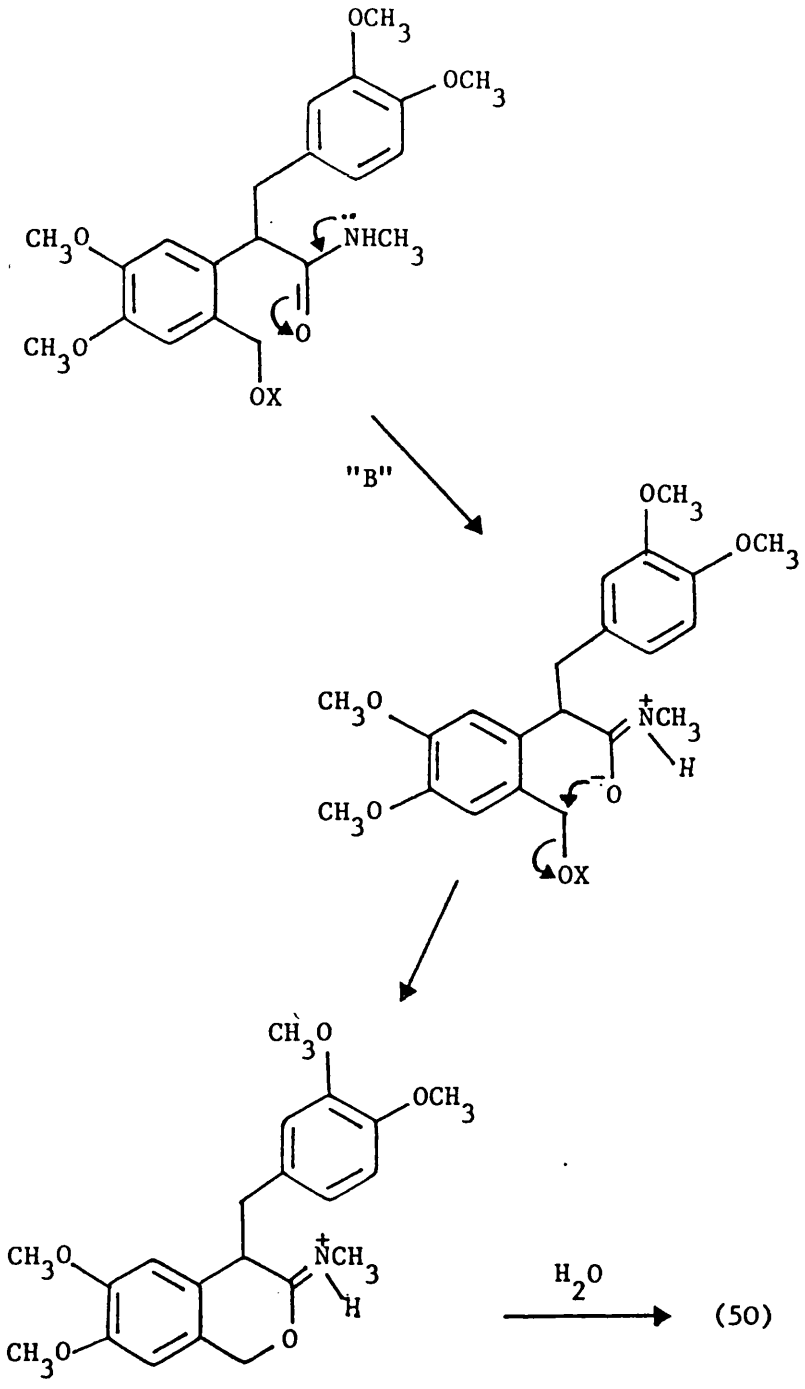
(97)

In order to circumvent these problems my colleague M. Carmody[14] ring-opened the 4-benzylisochromanone (50) with methylamine[15] thus obtaining the amide alcohol (98)[36]. However, all attempts to cyclise this molecule and its O-acyl and O-sulphonyl derivatives[53] using a variety of acidic and basic reagents led either to the formation of an unwanted tricycle (99) or return of the original 4-benzylisochromanone (50). Such changes and possible mechanistic explanations

are summarised below:

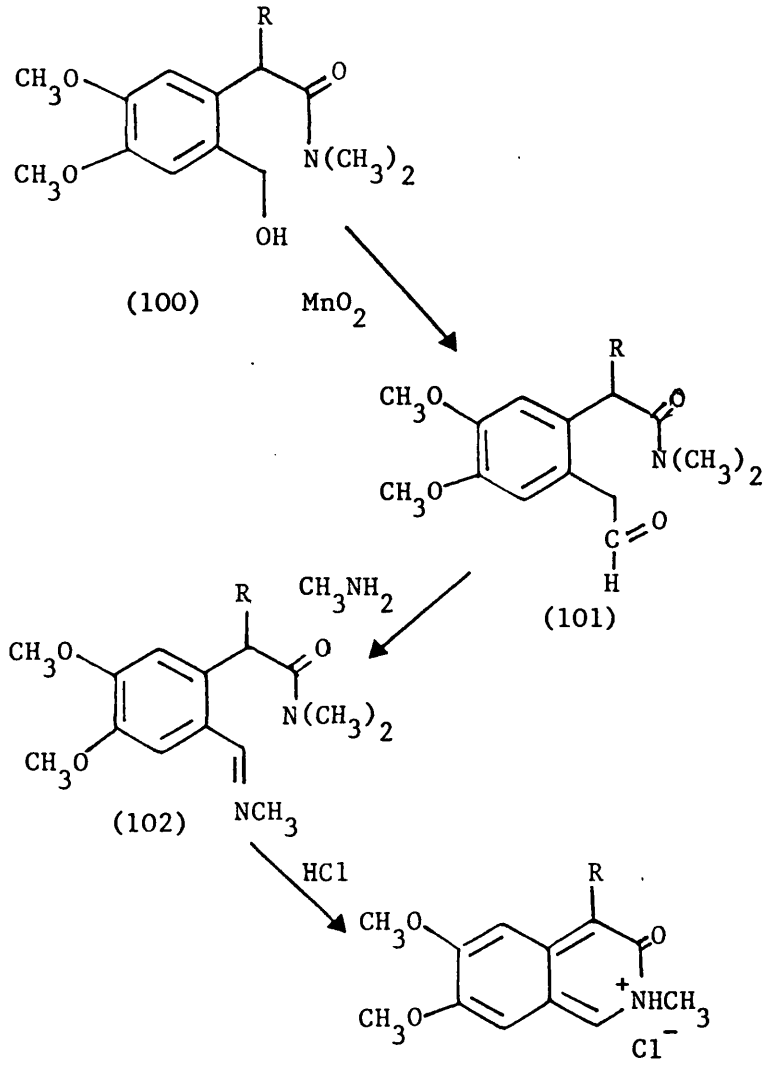


(99)



X = p-Toluenesulphonate

Workers at Glasgow[54] have successfully prepared 2H-6,7-dimethoxy-2-methyl-3-oxoisoquinolinium chloride (103, R = H) from the hydroxamide (100, R = H), first by oxidation to the aldehyde (101, R = H), then treatment of this product with methylamine to give the iminoamide (102, R = H), and finally acid promoted ring-closure.

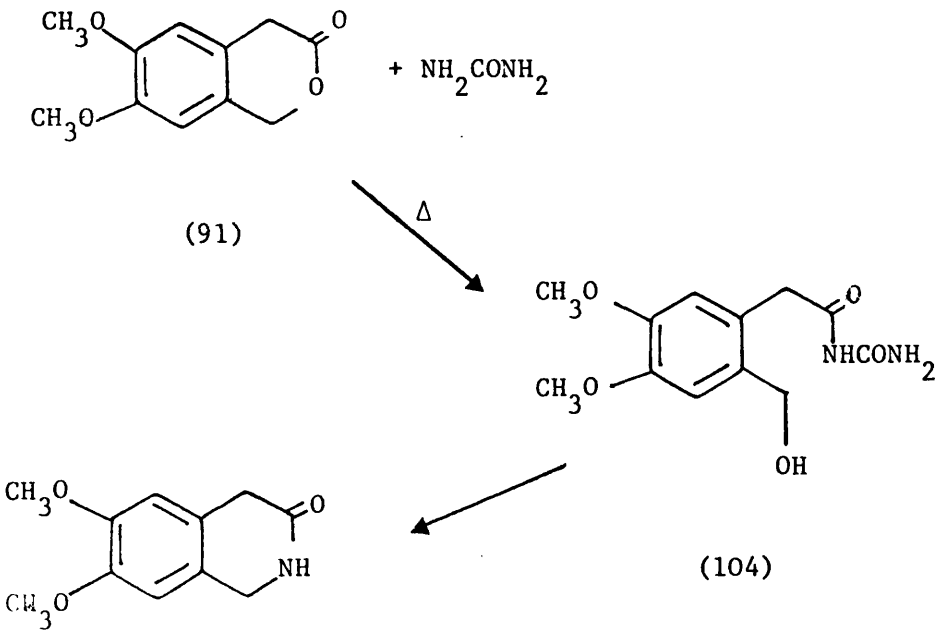


(103)

R = H, $CH_2C_6H_3(OMe)_2$-3,4

This sequence was repeated by Carmody now with analogue (100, R = $CH_2C_6H_3(OMe)_2$-3,4) as starting material[55,56]. He obtained the corresponding product (103, R = $CH_2C_6H_3(OMe)_2$-3,4) in good yield, but discovered that reduction of it to the desired compound (88) was difficult to carry out and led to unstable mixtures which he was unable to separate into pure product.

White[57] and his co-workers have shown that when the simple isochromanone (91) is heated with urea[58] the lactam (105) is formed. This is a rather unusual reaction for if the first phase is nucleophilic attack at the carbonyl group then it would be supposed that the urea derivative (104) would form. From this point it is difficult to see how ring-closure to the lactam (98) can occur (see p. 111,112).



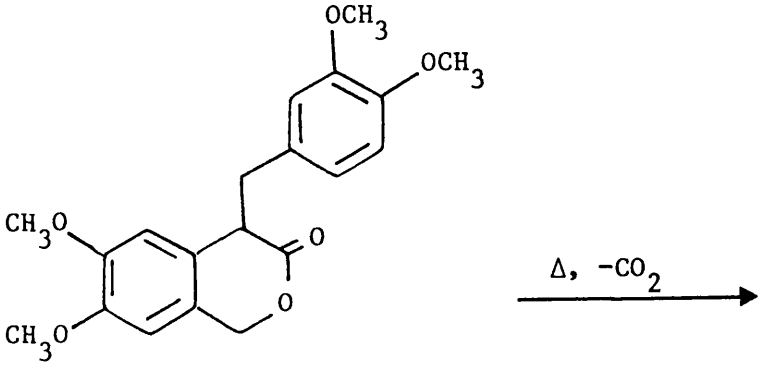
(91)

(104)

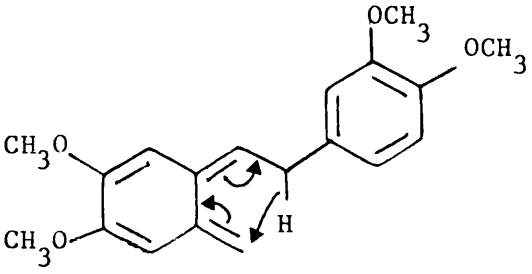
(105)

In the authors hands when the 4-benzylisochromanone (50) was heated with urea under identical conditions a product was obtained which contained no nitrogen. From the data of the ^1H n.m.r. spectrum it was soon apparent that the structure of this product was that of the trans-stilbene (108) and this was confirmed by consideration of the ultraviolet and infrared spectral data and by elemental analysis.

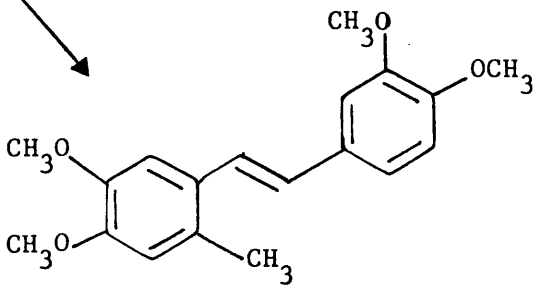
A likely explanation is that on heating isochromanones lose carbon dioxide, affording quinonedimethides (e.g. 106,107) which then trap available nucleophiles or rearrange. In the case of the simple isochromanone (91) it is possible that it traps cyanic acid, or an equivalent product from the thermolysis of urea. While in the more complex analogue (50) the intermediate (107) undergoes a sigmatropic [1,5]proton shift leading to the stilbene (108).



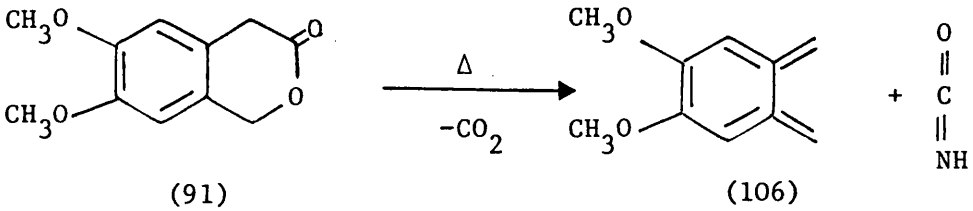
(50)



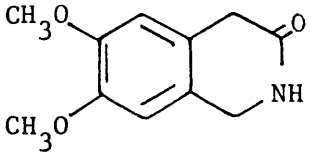
(107)



(108)

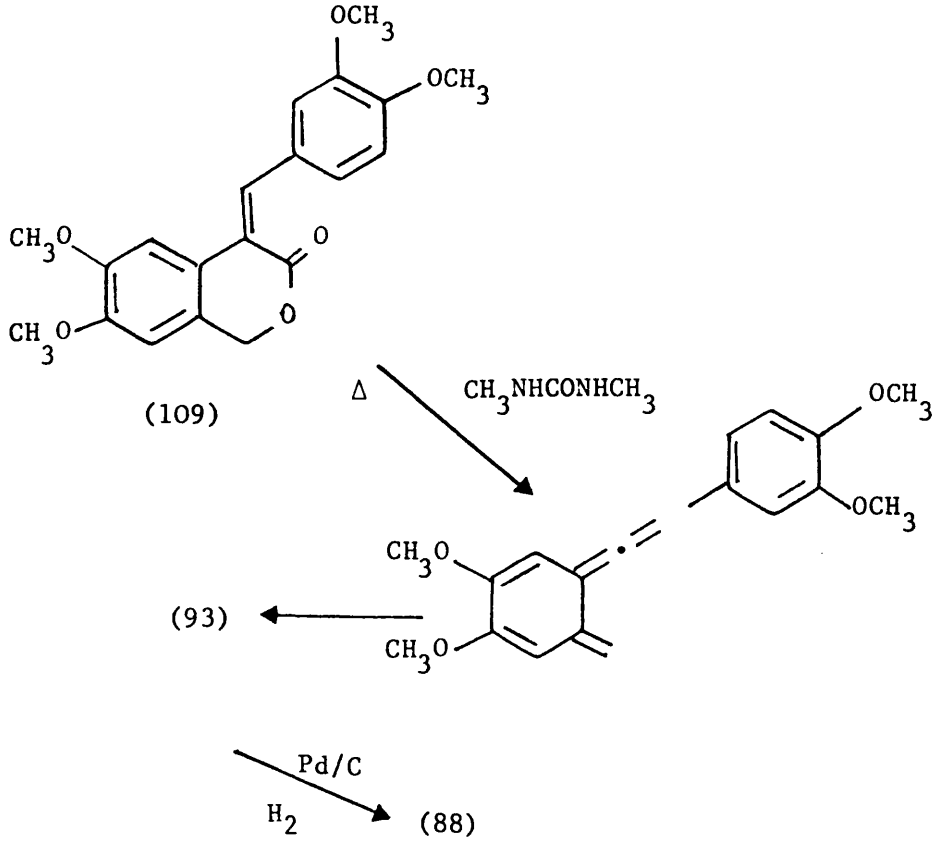


(91) (106)

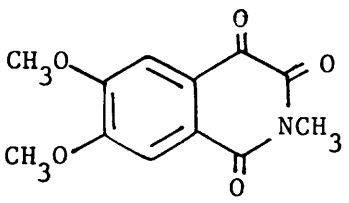


(105)

These results have generated a good deal of new work which now forms part of the postgraduate studies in this department of another student, G. Black[59]. He has, for example, made the urea derivative (104) and shown that it does not yield the simple isoquinolinone (105) on thermolysis. More importantly he has solved the synthetic problem relating to the production of the 4-benzylisoquinolinone (88) by heating the mixed isomers of the 4-benzylideneisochromanone (109) with N,N'-dimethylurea. This treatment affords the product (93) which on reduction gives the required substrate (88), albeit in modest yield (10% overall).



Sadly after all this effort an anodic oxidation of the 4-benzylisoquinolone did not give a coupled product, instead the substituent group was cleaved off and the trione (110) formed in very high yield. This happened in three separate experiments and my colleague has not yet found the enthusiasm to repeat the electrolysis again.



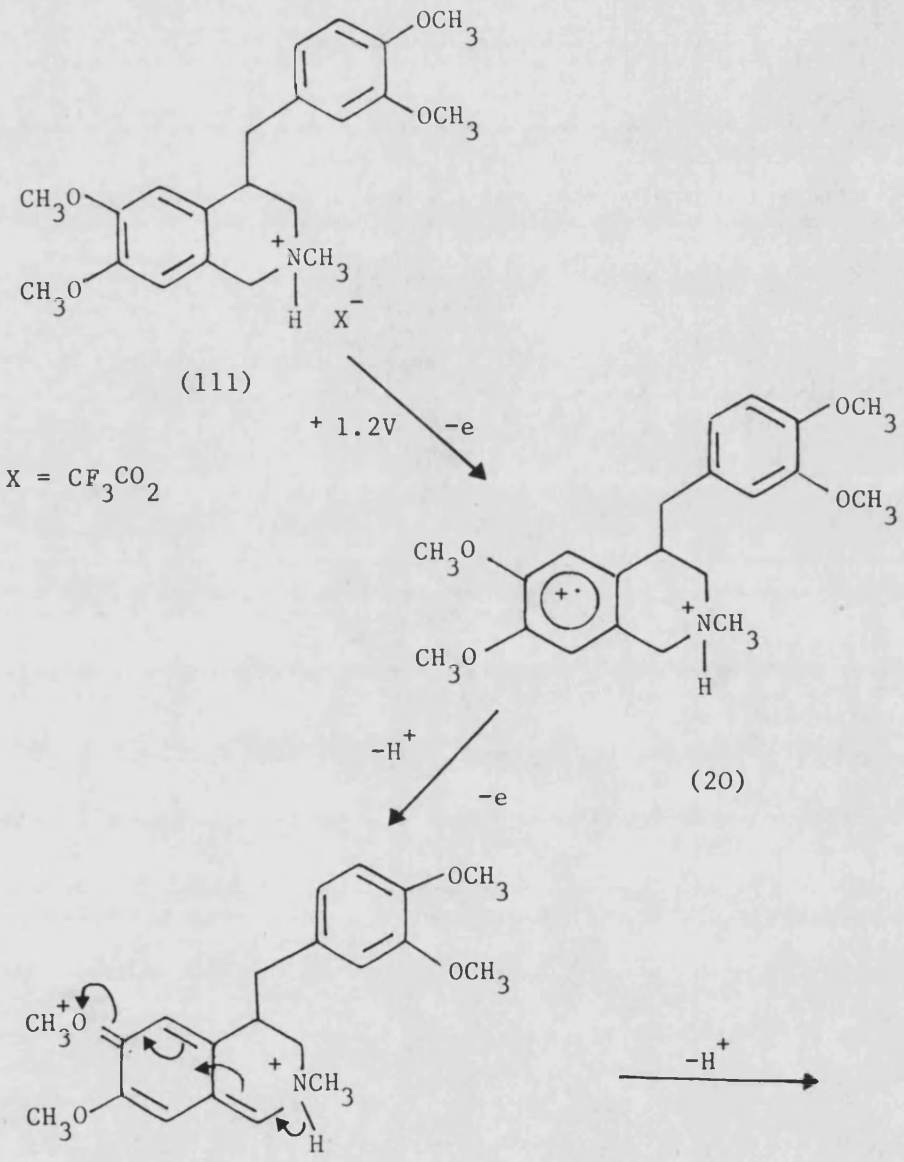
(110)

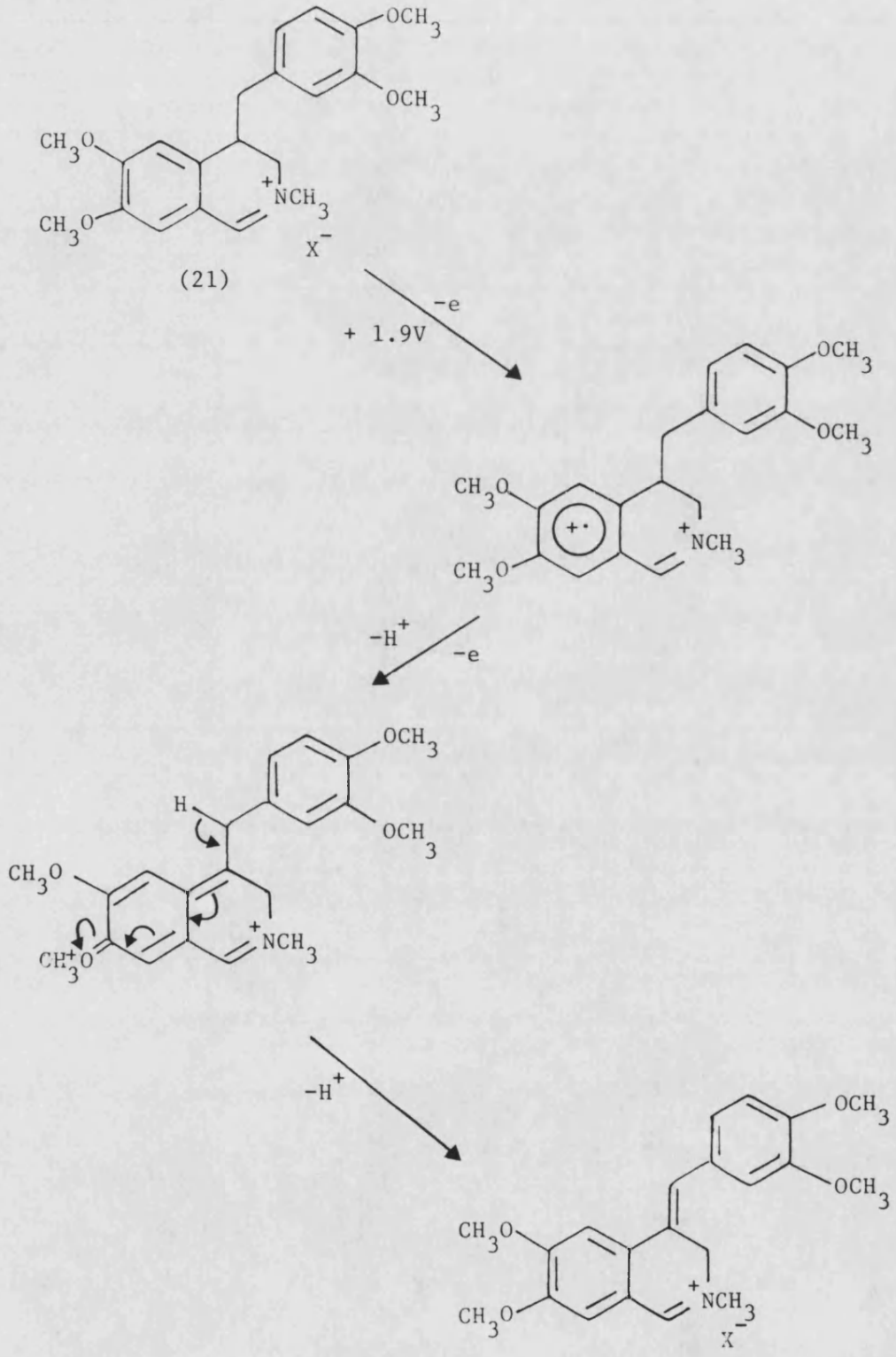
(vi) The oxidation of 4-benzyltetrahydroisoquinolines

An obvious solution to the difficulties experienced in this work is to change the nature of the substrate for anodic oxidation. For example, as long as the nitrogen atom is rendered non-basic, 4-benzyl-1,2,3,4-tetrahydroisoquinolines (16) could be used. Preliminary studies by Carmody[1] on the salt (111) were, however, not encouraging for internal oxidation took place rather than intramolecular coupling. Two products (21) and (22) were obtained and it is assumed that these formed by a mechanism of the type

shown in Scheme 6.

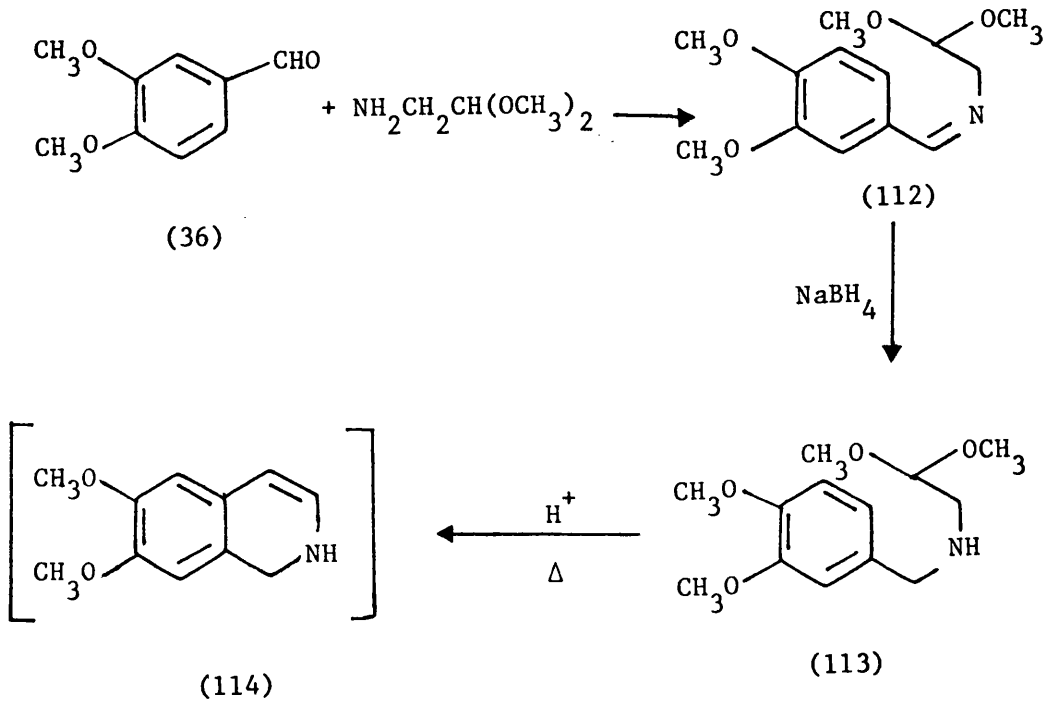
Scheme 6

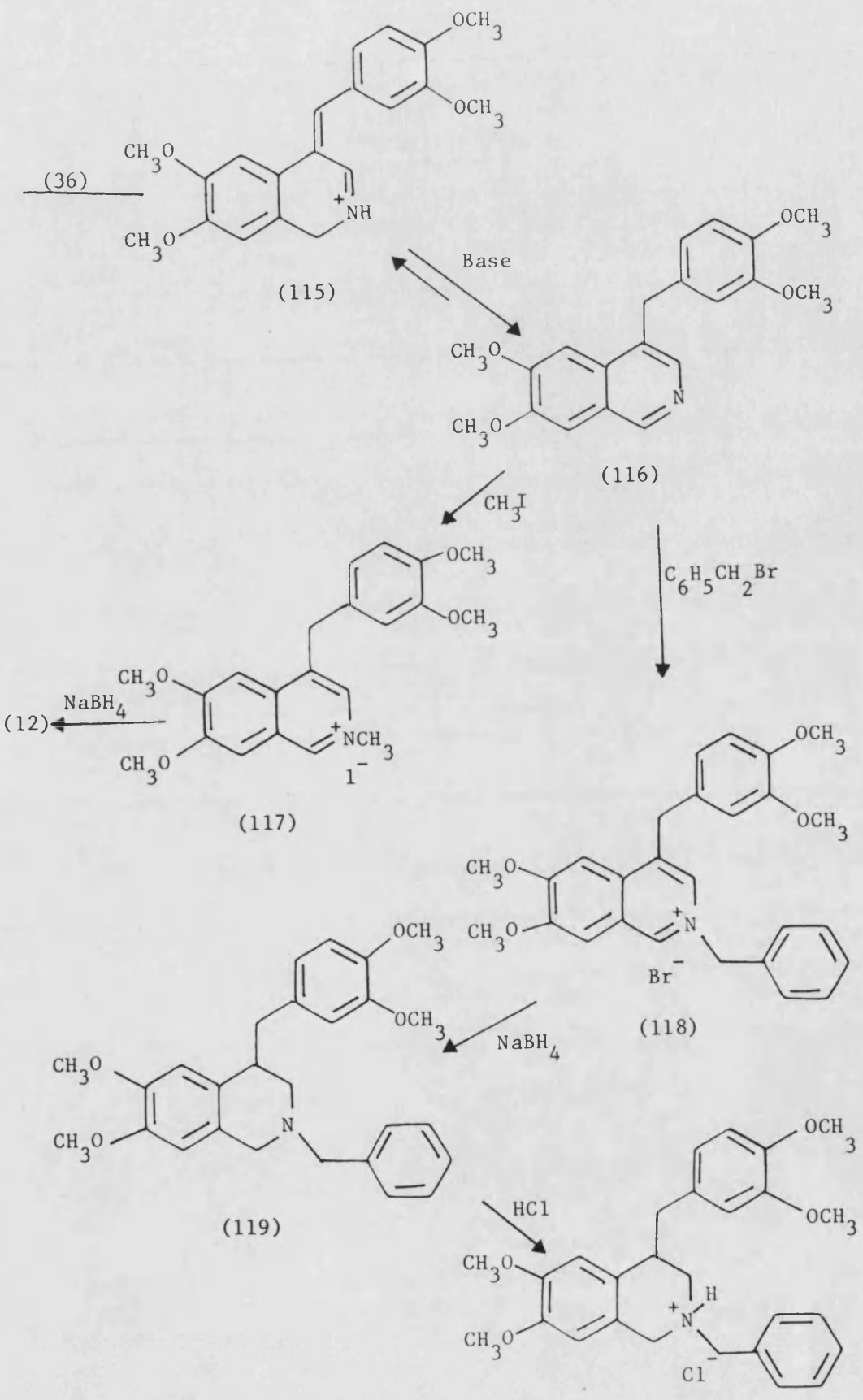


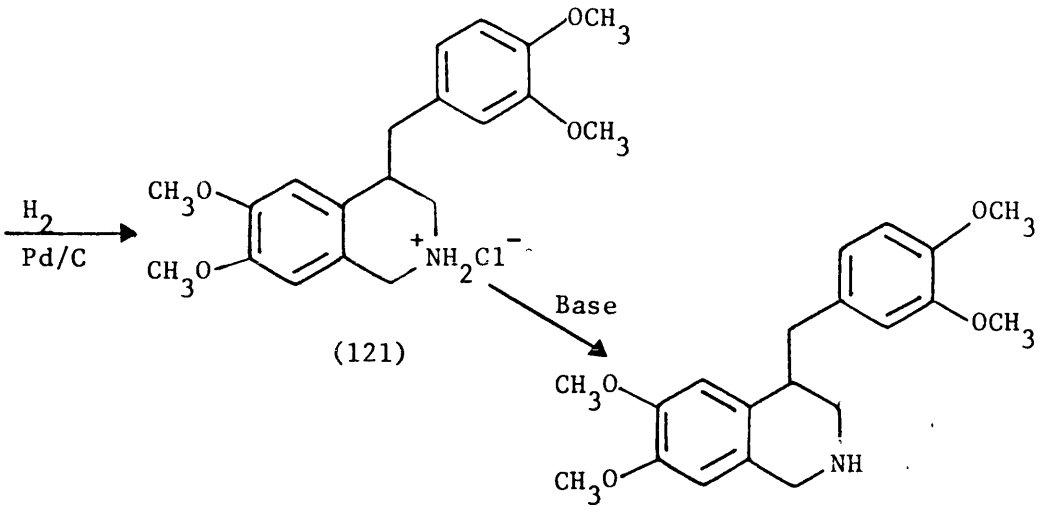

OCH3
OCH3
CH3O
CH3O
+NCH3
X−
(21)
-e
+ 1.9V
+·
-H+
-e
H
CH3O
CH3O
+NCH3
-H+
(22)

Schäfer and his co-workers[46] have shown that in the 1-benzyltetrahydroisoquinoline series a change in the nature of the electrolyte has an effect on the electrolysis products (see p. 91) Thus as a rather speculative first entry into the use of 4-benzyltetrahydroisoquinolines, as substrates for anodic oxidation, the author's task was to make the dimethoxylated derivative (125) and to study its coupling reactions in a variety of electrolytes. The usual synthesis of 4-benzyltetrahydroisoquinolines involves the formation of the appropriate 1,2-dihydroisoquinoline (114) in situ and its reaction with aldehydes. The preparation of the tetramethoxylated compound (122) is illustrative and was in fact repeated several times by the author in later work (Scheme 7) (see p.131).

Scheme 7.



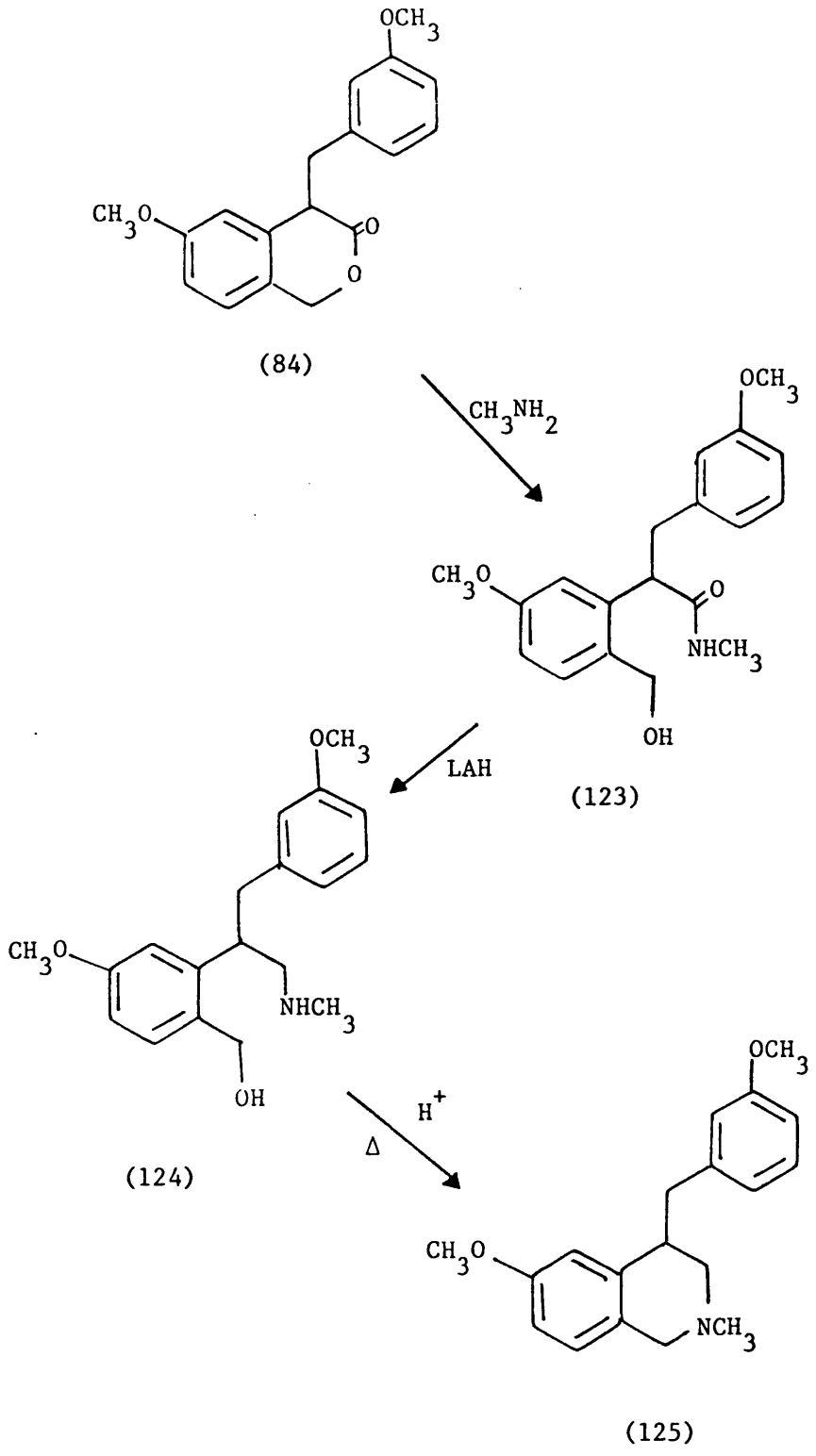

(36)
(115)
Base
(116)
CH3I
C6H5CH2Br
NaBH4
(12)
(117)
(118)
NaBH4
(119)
HCl
(120)



(122)

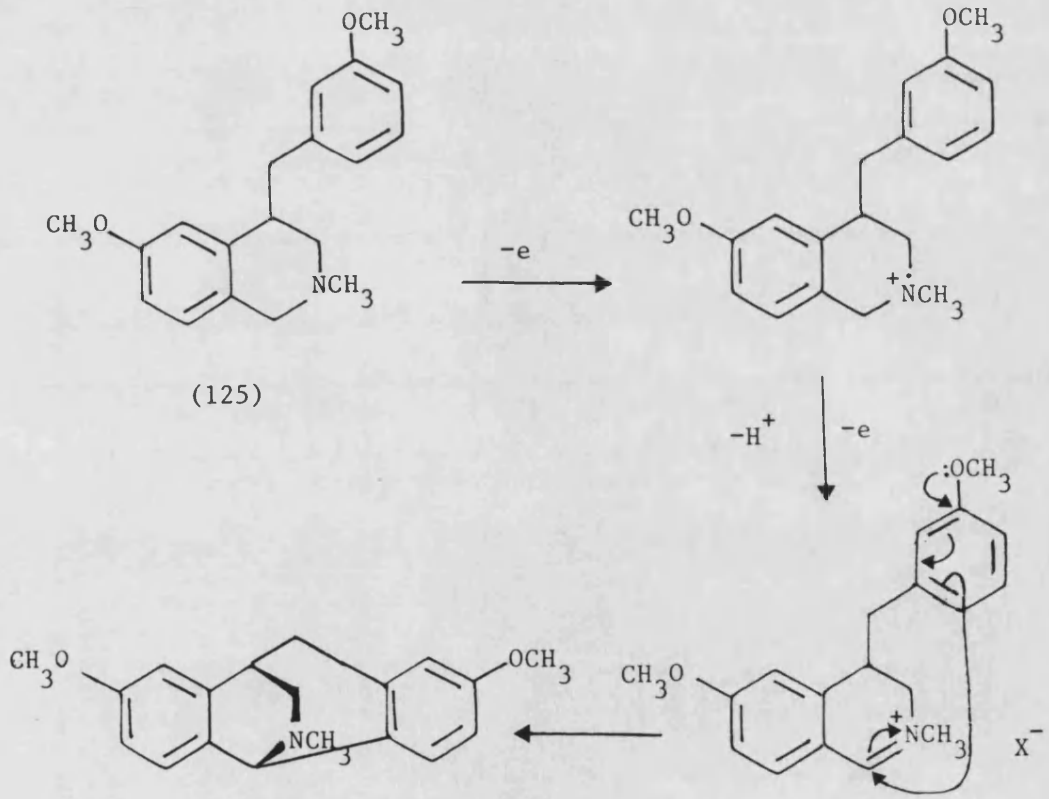
This route is restricted to 7-alkoxylated (or 7-hydroxylated) structures for if this activational substituent is absent ring-closure to the 1,2-dihydroisoquinoline derivative (114) fails. For this reason we were forced to devise a new approach in the synthesis of the dimethoxylated compound (125). This is outlined in (Scheme 8). Having obtained the isochroman-3-one (84) by the usual route, ring-opening was effected by reaction with methylamine to give the amido alcohol (123), which was then converted into the corresponding amine (124) by reaction with lithium aluminium hydride. Cyclisation to the required tetrahydroisoquinoline was achieved by heating the hydroxy amine with p-toluene sulphonic acid in benzene.

Scheme 8.


OCH3
CH3O
O
O
(84)
CH3NH2
OCH3
CH3O
O
NHCH3
OH
(123)
LAH
OCH3
CH3O
NHCH3
OH
(124)
H+
Δ
OCH3
CH3O
NCH3
(125)

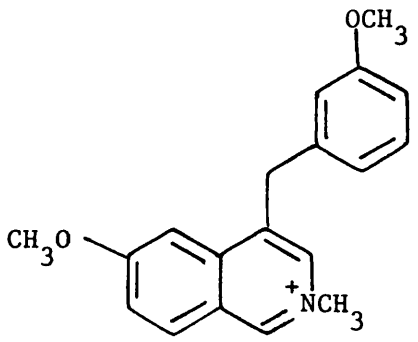
This product was now electrolysed at +1.5 volts in a solution of acetonitrile:methanol (3:1) containing sodium perchlorat as supporting electrolyte. Interestingly none of the expected salt (126) was isolated, instead a low yield of the tetracycle (127) was obtained, after repeated chromatography of a tarry product.

It is possible that the formation of this new tetracycle is related to the previous work (cf. Scheme 6) for an intermediate cation, such as (126) is most likely to be involved which is then trapped by the π-electrons of the 4-benzyl substituent.

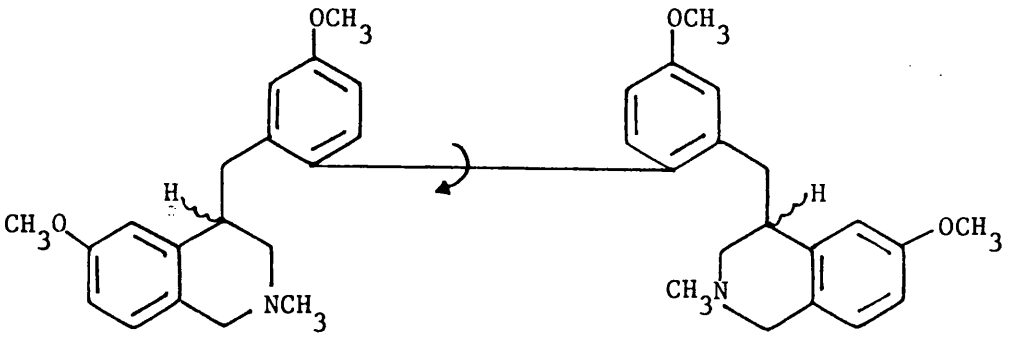


X = ClO_4

The low yield of isolated product points to other processes occurring at the same time, so that it is likely that alternative structures such as the water soluble salt (128) were "lost" during work up. The question now was would this particular dimethoxylated isoquinoline (125) undergo a similar reaction in acidic media, thus making a direct comparison with Carmody's work? In practice it did not, for when fluoroboric acid was added to the electrolyte prior to the anodic oxidation, the only compound formed was the dehydrodimer (129) (present as a mixture of diastereomers).



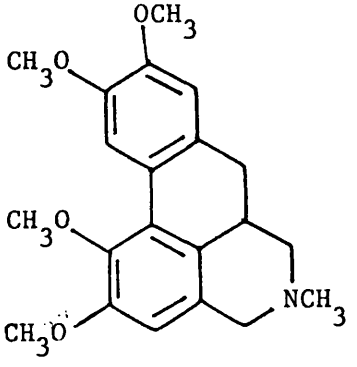
X = ClO_4 (128) X^-



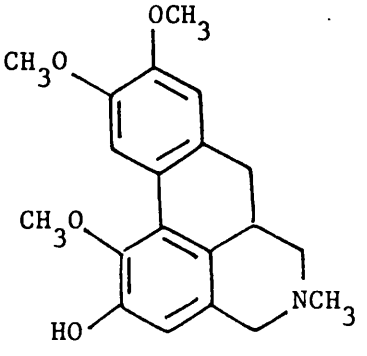
(129)

It is reasonable to conclude therefore, that in the protonated form of the substrate, oxidation of the 4-benzyl-substituent is more easy than that of the aryl ring adjacent to a positively charged centre. It is to this ring that intermolecular coupling is then directed provided the substrate concentration is high enough. [Incidentally a similar mixture of diastereomeric dehydrodimers (23) was also obtained by Carmody during the oxidation of the tetramethoxylated isoquinolinium salt (111)].

In parallel with the author's study an undergraduate student Premji Patel[60], was re-examining Carmody's work. He was able to show that when methanol and acid are added to the electrolyte the tetramethoxyisoquinoline (16) affords small amounts of the two isoaporphines (130) and (131), but only if the substrate concentration is sufficiently low to disfavour intermolecular attack.

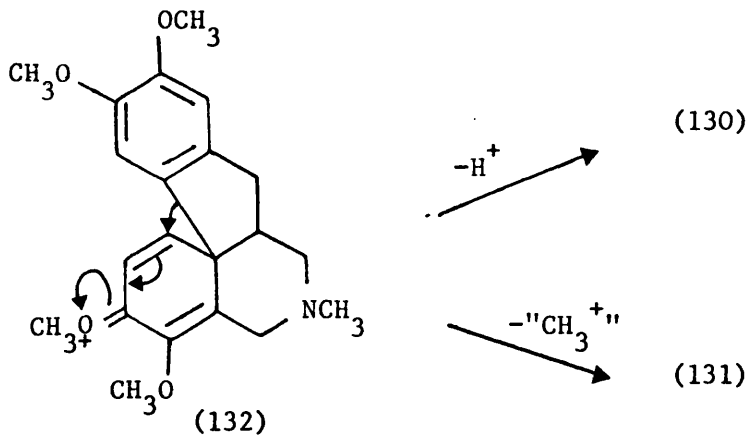


(130)

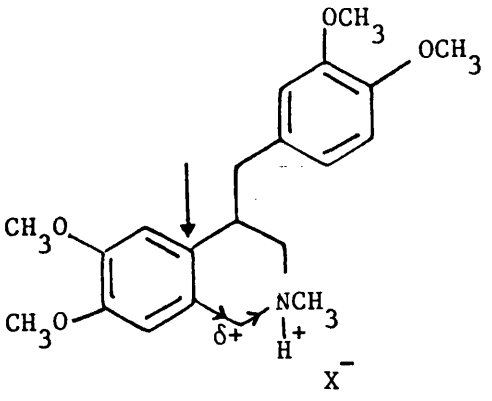


(131)

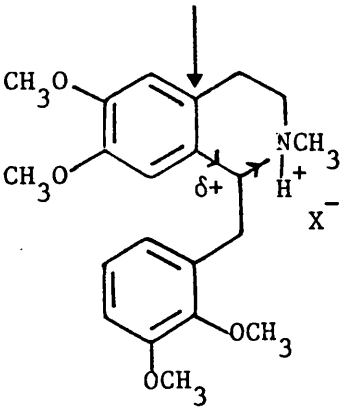
The structures of the isoaporphines are interesting, and, for example, the tetramethoxy compound[61] may form either directly through ortho-para coupling (C-5, C-'6), or by para-para union (C-4a, C-'6), followed by rearrangement. The first pathway may be regarded as a favoured 6-endo-trig reaction, but anodic ortho-para coupling with respect to aryl methoxy groups is a rare event. Equally the alternative route requires an initial 5-endo-trig cyclisation which is also uncommon[62]. Strong circumstantial evidence in favour of the latter process is provided by the fact that the isoaporphine (131) is phenolic. Thus it is reasonable to suggest that both structures (130) and (131) derive from a common intermediate (132), and in the formation of the hydroxylated product, O-demethylation precedes dienone-phenol rearrangement. From these results it seems probable that N-protonation of 4-benzyltetrahydroisoquinolines sets up an inductive effect which inhibits intramolecular coupling to C-8a but allows attack at C-4a and the formation of "unusual" structures such as the isoaporphines (130) and (131).



The same effect in 1-benzyltetrahydroisoquinolines [see structures (133) and (134)] such as laudanosine (12), complements the kinetically favoured 6-endo-trig process leading from coupling at C-4a on to morphindienones exemplified by O-methylflavinantine (13)[9,63]. However, when 1-benzyltetrahydroisoquinolines (12) are oxidised in neutral media they also yield neospirodienones (135)[64].

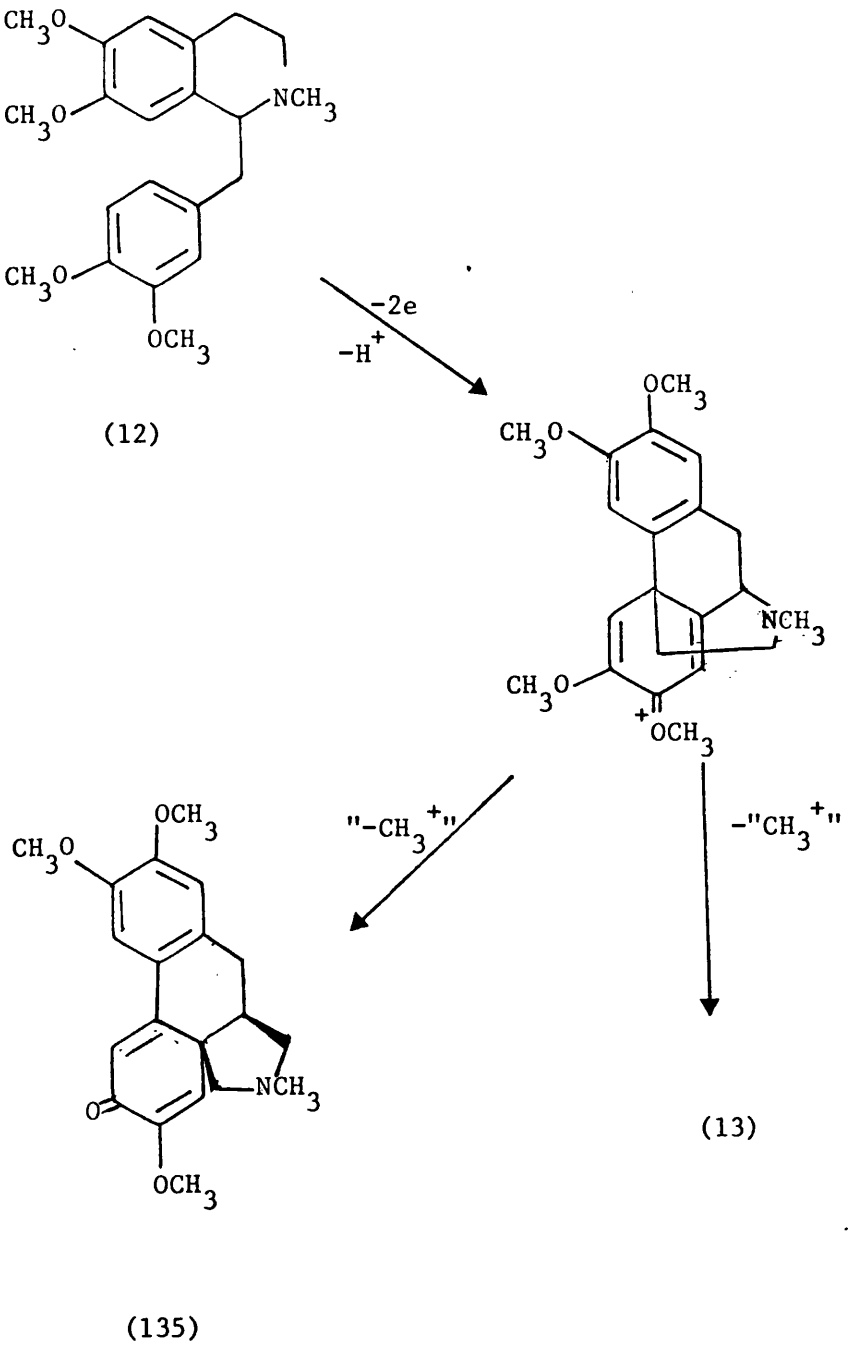


(133)



(134)

(arrows denote position of coupling onto the heterocyclic system)

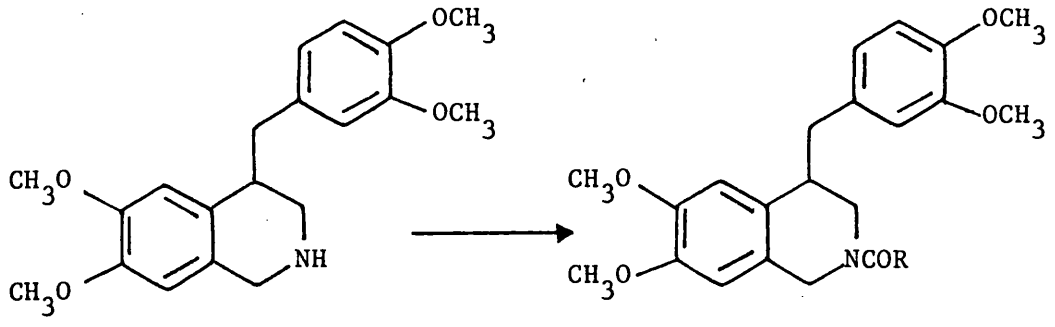

CH3O
CH3O
NCH3
CH3O
OCH3
-2e
-H+
OCH3
CH3O
NCH3
CH3O
+
OCH3
"-CH3+"
-"CH3+"
CH3O
OCH3
NCH3
O
OCH3

(12)

(13)

(135)

Preliminary attempts to oxidise at low concentration the dimethoxylated tetrahydroisoquinoline (125) in acidic media did not appear promising since much tar was formed. So we consider that N-protonation of the 4-benzyl-1,2,3,4-tetrahydroisoquinolines is not useful in achieving the desired type of intramolecular coupling. Next the author set about the synthesis of the N-acyl derivatives (136, R = H) and (136, R = CF_3)[12] of the tetramethoxylated-4-benzyltetrahydroisoquinoline. These structures were obtained from the N-benzyl derivative (119) (see Scheme 7), followed by de-N-benzylation ($Pd/C/H_2$) and acylation of the product (122) either with trifluoroacetic anhydride or acetic formic anhydride.

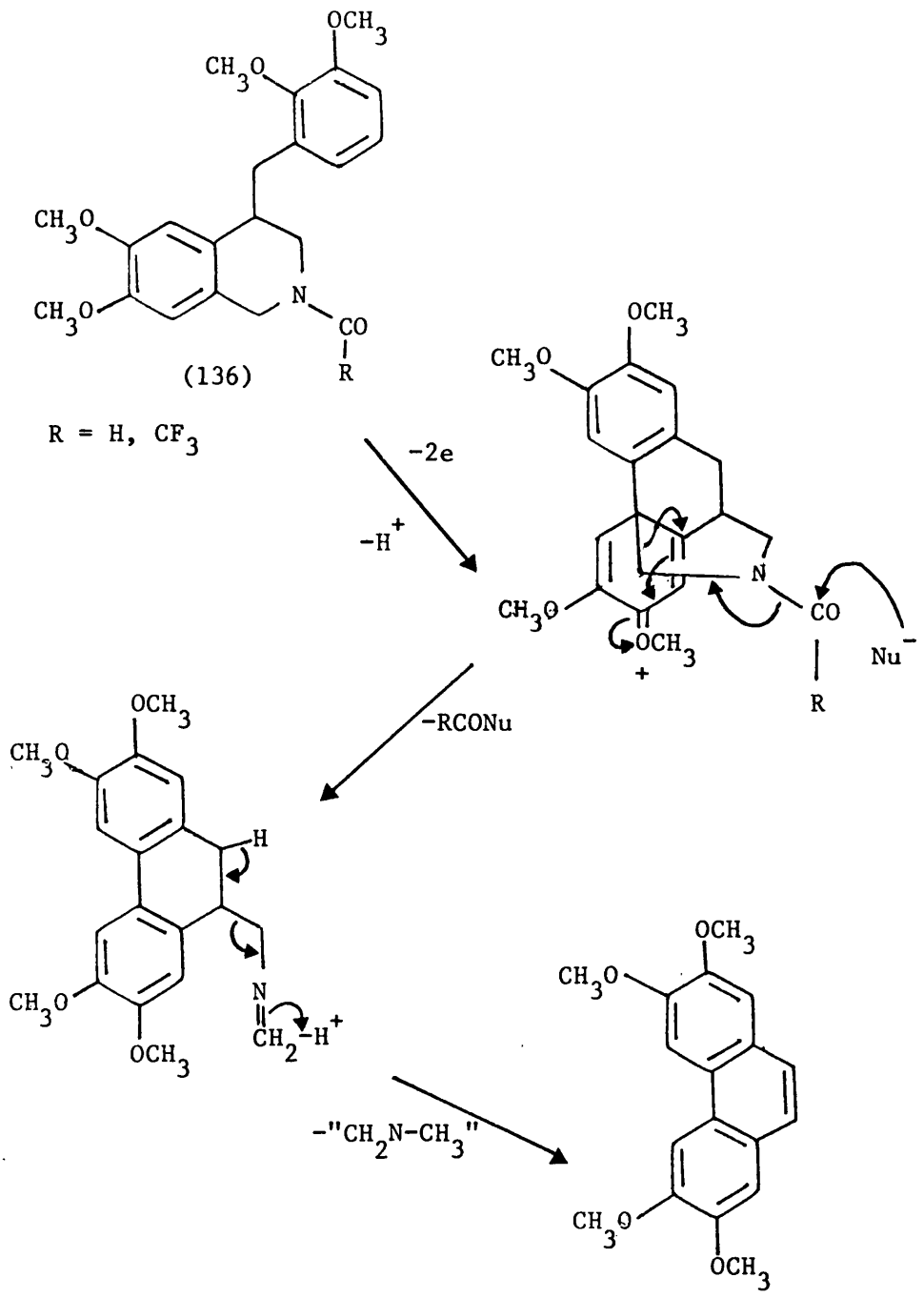


(122) (136)

R = (H, CF_3)

Anodic oxidation of these compounds in separate experiments gave the same product, namely the tetramethoxyphenanthrene (137). Disappointing as these results were they indicated that the correct mode of coupling had taken place, but that on work up

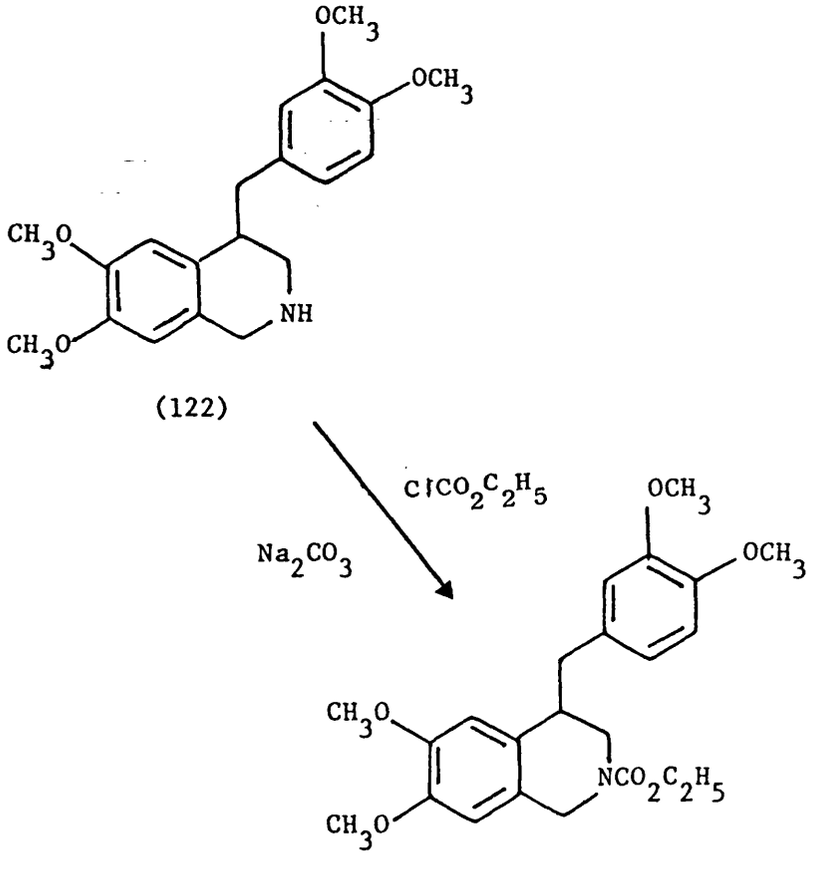
(or perhaps before) a disruptive aromatisation process occurs. A possible mechanism is shown below:



(136)

(137)

If this is so then the degradative process is triggered off by attack of an available nucleophile and clearly a less electrophilic protecting group is required. We then prepared the N-ethoxycarbonyl derivative (138), by reacting the tetrahydroisoquinoline (122) with ethyl chloroformate and sodium carbonate. The cyclic voltammogram (Fig. 5) of this compound is relatively simple and shows an electron loss at +1.28 volts. Further oxidation occurs at +1.7 volts, although at this voltage the nature of the process is rather less precise giving rise to a broad band.

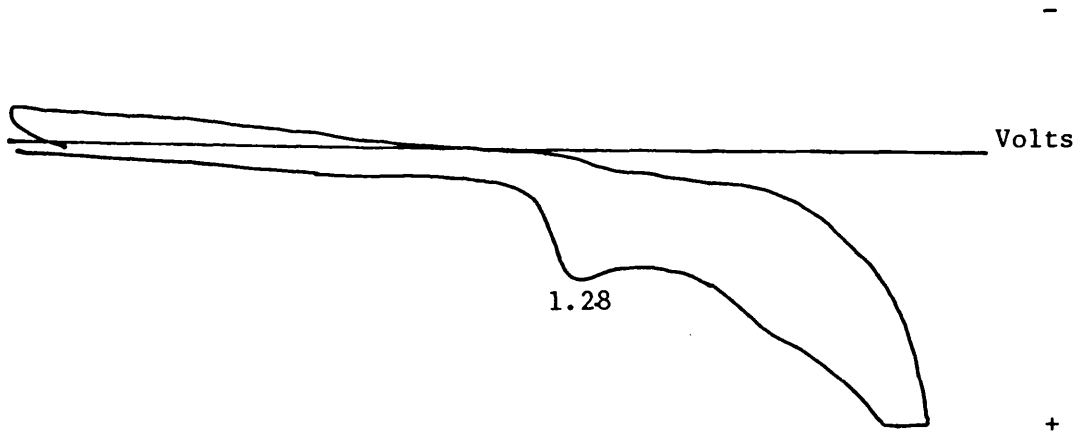


(122)

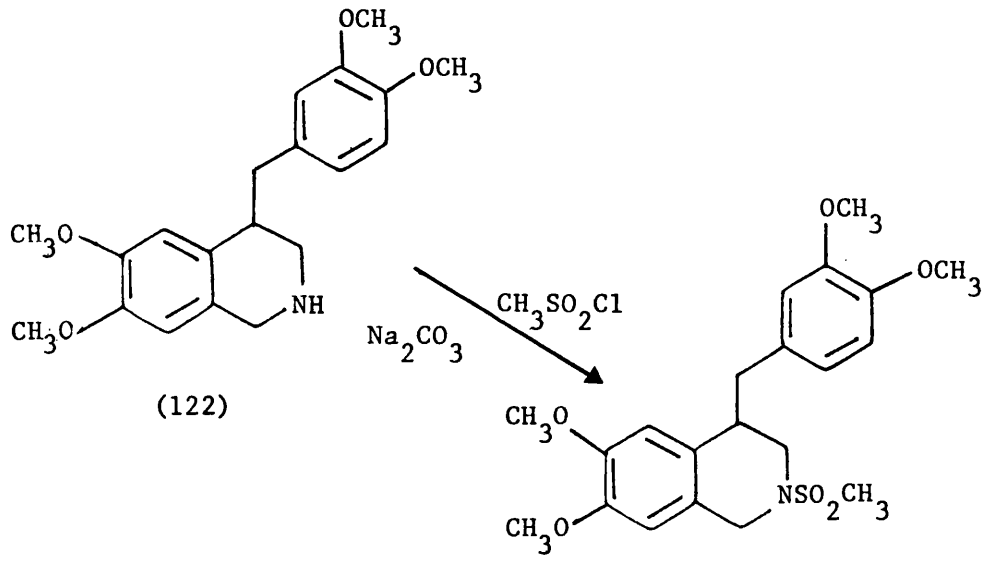
(138)

Figure-5

Cyclic voltammogram of N-(ethoxycarbonyl)-4-(6,7-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (138).



This result looked very encouraging since the anodic peak at +1.28 volts probably corresponds to the formation of a radical cation(s) associated with the aryl nuclei. Furthermore, the absence of a reduction peak at, or near, this value shows that the radical cation rapidly forms a product. However, in a preparative experiment, carried out in acetonitrile/sodium perchlorate as electrolyte at an anode potential of +1.3 volts, this compound also led to the production of the tetramethoxyphenanthrene (137). Next the N-phenylsulphonyl derivative (139) of the tetrahydroisoquinoline was synthesised by treatment of the tetrahydroisoquinoline (122) with methylsulphonyl chloride and sodium carbonate.



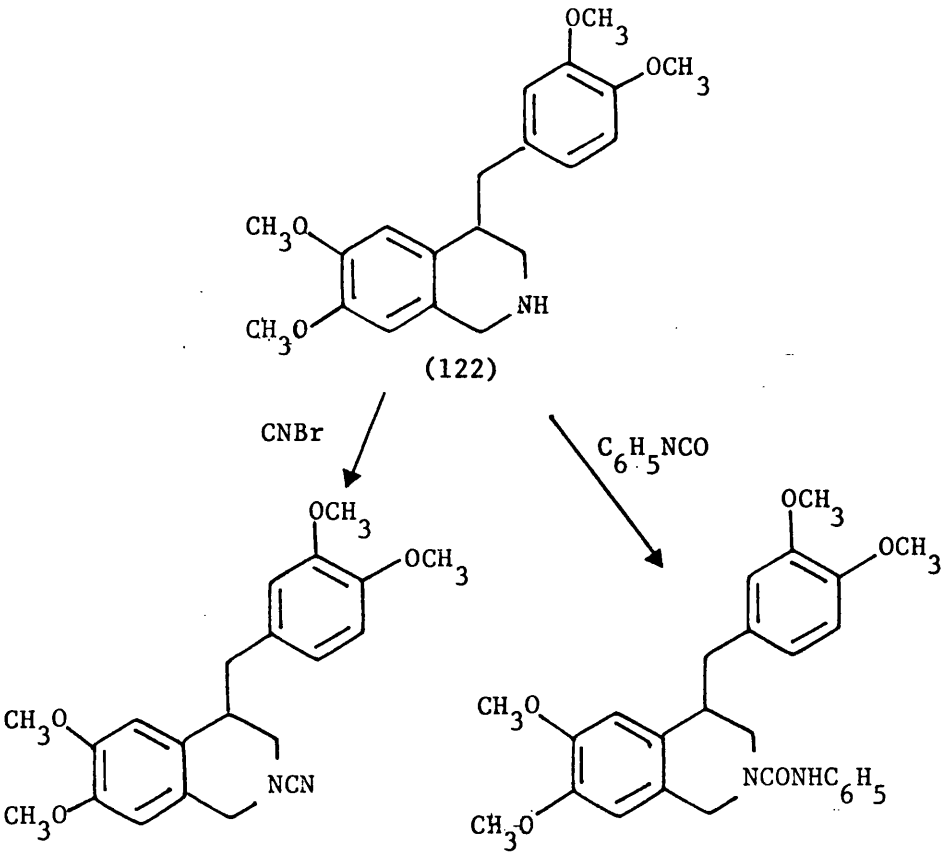
(122)

(139)

Once more an anodic peak at ≃+1.3 volts is evident in the cyclic voltammogram, but a preparative electrolysis at this potential led to a very complex mixture of products, from which only a dehydrodimer (as a mixture of diastereomers) could be isolated. In this product the points of union are through

C-6' of the 4-benzyl substituent.

The N-cyanotetrahy-(140) and N-phenylcarbamoyl-(141) derivatives of the tetramethoxytetrahydroisoquinoline were also made. The first by careful reaction with cyanogen bromide and the second by reaction with phenylisocyanate.



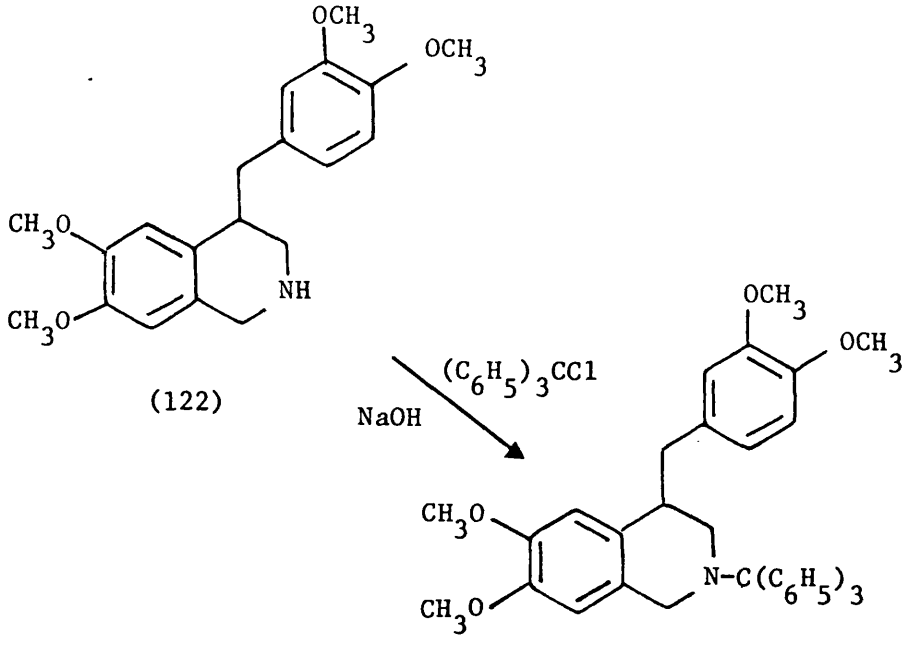
(140) (141)

The cyclic voltammograms of both compounds show the first anodic peak to occur at ≃+1.3 volts and the shape of the traces are similar to that of the N-sulphonyl derivative.

Electrolyses of either of these compounds under a wide variety of conditions did not yield the desired types of products, instead tars formed, but interestingly when attempts were made to oxidise them in very dilute solution mainly starting materials were returned. In summary then it seems that the presence of an electron withdrawing group on the nitrogen atom of 4-benzyltetrahydroisoquinolines or N-protonation causes a deactivation of the adjacent benzenoid ring especially at C-8a. At high substrate concentrations the result is intermolecular coupling *via* the 4-benzyl-substituent, and at high current densities oxidation to salts such as 3,4-dihydroisoquinolinium or isoquinolinium species (see Scheme 6). Related structures such as the tetracycle (17) may also form. At low substrate concentrations intramolecular aryl-aryl coupling does take place in certain cases, but now at C-4a, even though this formally represents an example of the kinetically disfavoured *5-endo-trig* type cyclisation. A case where geometrical preferences are over-riden by electronic demands.

One last attempt was made to overcome these problems and to achieve intramolecular aryl coupling to C-8a. We argued that if the nitrogen atom is basic then N-C coupling usually takes place, because initial electron loss occurs from the nitrogen lone pair. Should, however, the nitrogen atom be substituted by a bulky group N-C coupling might be inhibited and the desired reaction course might then be followed. To this end the N-triphenylmethyl derivative

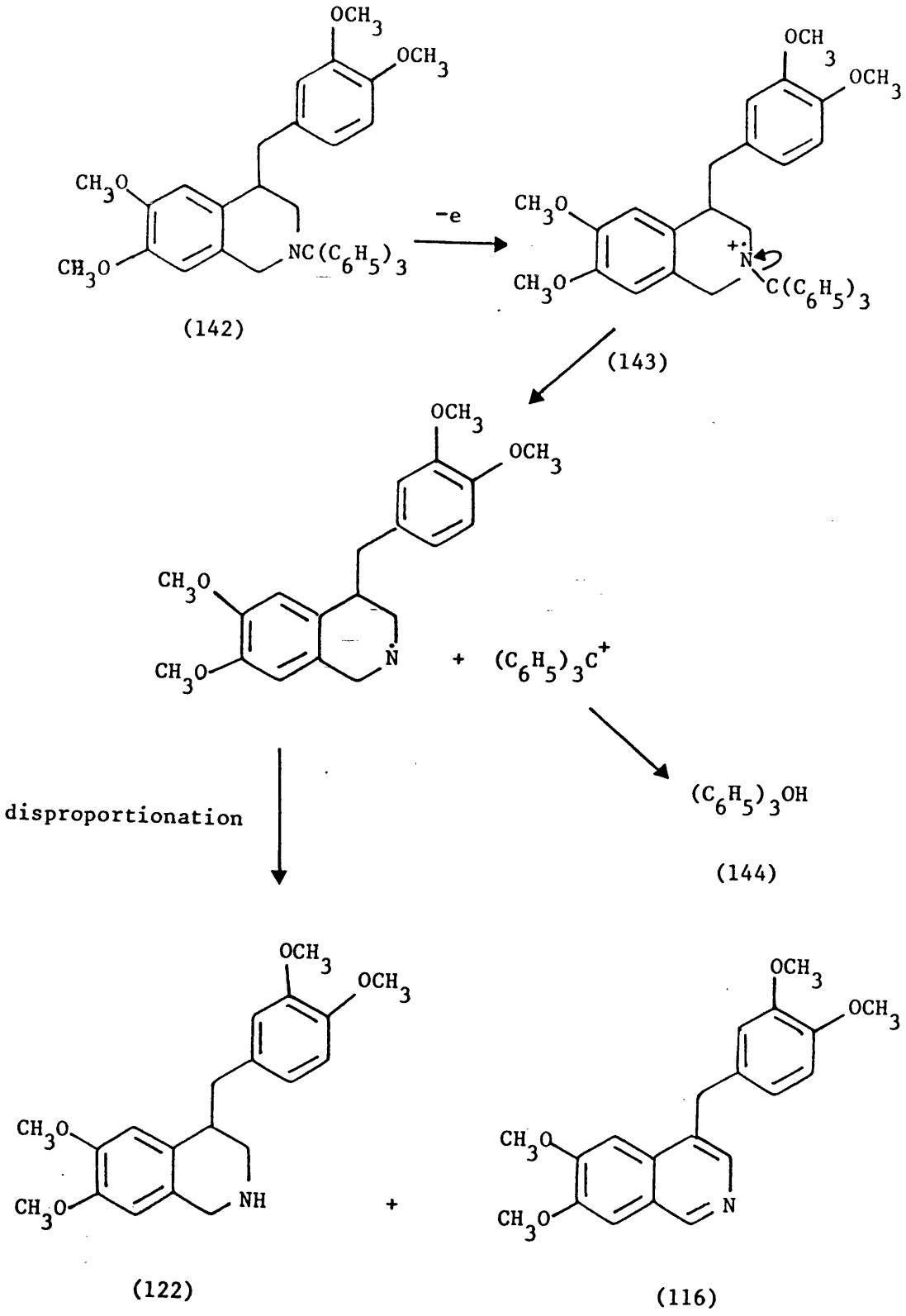
(142) was made by reacting the tetrahydroisoquinoline (122) with triphenylmethyl chloride in the presence of sodium hydroxide.



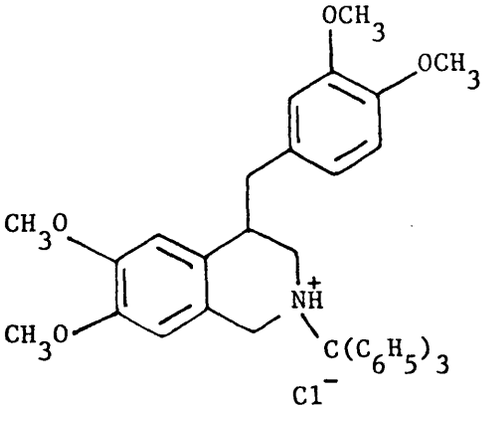
(142)

Electrochemical oxidation of this product in acetonitrile containing sodium perchlorate and at the anode potential of + 1.2 volt gave a starting 4-benzyltetrahydroisoquinoline (122) and triphenyl methanol (144).

Clearly the radical cation (143) is produced and this leads on to N-dealkylation perhaps as shown on the following page. (The origin of the tetrahydroisoquinoline (122) is uncertain. It may arise from a disproportion mechanism or through proton extraction from an available donor). If the disproportionation sequence operates.


OCH3
OCH3
CH3O
CH3O
NC(C6H5)3
-e
(142)
(143)
+
(C6H5)3C+
(C6H5)3OH
(144)
disproportionation
NH
N
(122)
(116)

A missing product is the isoquinoline (116), but we were not able to obtain this structure in a pure form from this experiment. However, when the oxidation was repeated now on the hydrochloride salt (145) both the isoquinoline (116) and the tetrahydroisoquinoline (122) were isolated (as salts) and fully characterised.

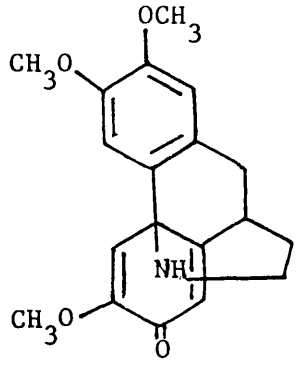


(145)

We use this circumstantial evidence to argue the disproportionation mechanism for the first process and it is likely that if the first experiment were to be repeated again the "missing" isoquinoline would be detected, but lack of time precluded this work. The struggle is not yet over, however, and another research worker in this department will study the oxidation of some N-fluoroalkylated substrates in the hope that the desired reactions can be promoted.

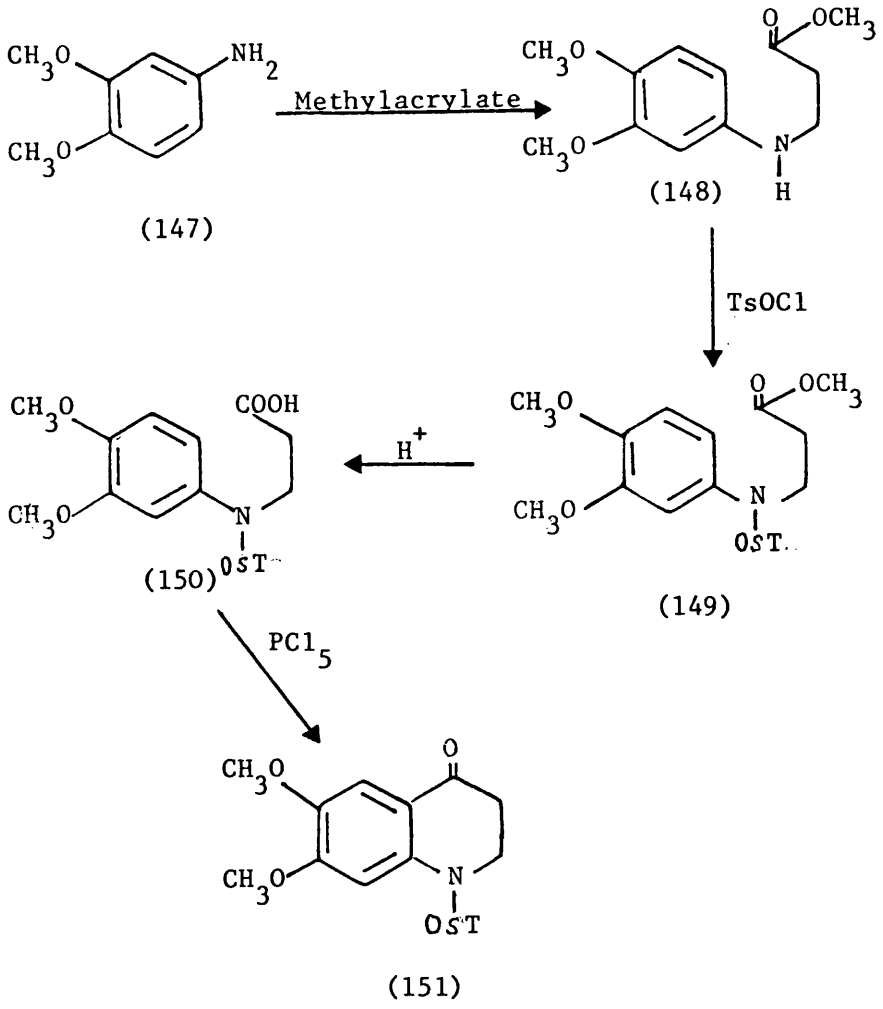
vii. Preliminary work concerning the synthesis and oxidation of 4-benzyltetrahydroquinolin-3-ones

The final topic to be described in this thesis is some preliminary studies directed towards the electrochemical synthesis of the alternative isomorphinan structure (146).



(146)

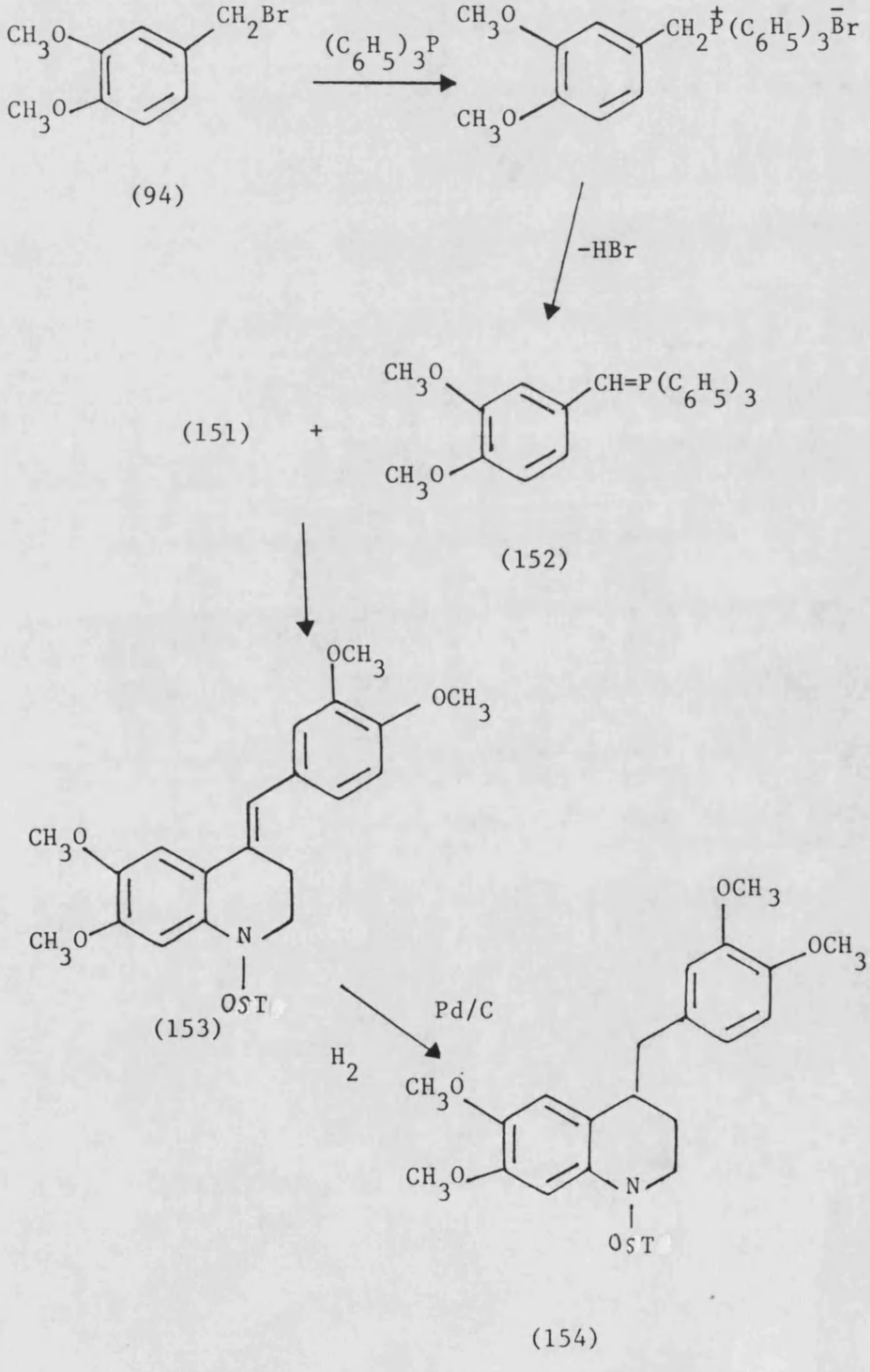
The appropriate substrate for this may be the tetrahydroquinoline (154) and we set about its synthesis in the following way.[65] 3,4-Dimethoxy aniline (147) was reacted with methyl acrylate in boiling benzene to give the ester (148). This product was then N-tosylated with p-toluene sulphonyl chloride and hydrolysed to the acid (150) with potassium hydroxide solution. This was then cyclised to the quinolinone (151)[66] by phosphorus pentachloride.



TsOC1 = P-Toluenesulphonylchloride

We hoped that a Wittig type[67] reaction on this substance would afford the benzylidene derivative (153) which could be then reduced to the benzyltetrahydroquinoline (154), but in practice this reaction failed with the ylide (152) derived from the phosphorane of 3,4-dimethoxybenzyl bromide (94) and triphenylphosphine.

More reactive ylides are known to react with ketones and further work will be undertaken in this department to investigate this type of reaction at a later date.



EXPERIMENTAL

General:

Melting points were recorded with an Electrothermal Mk.II apparatus, U.v. spectra were recorded on Perkin Elmer 402 and Lambda 3 spectrometers for solution in aqueous 95% ethanol, Perkin Elmer 197 or 1310 machines were used to record I.R. spectra and the data refer either to Nujol mulls or to solutions in Analar chloroform, as noted. ^{1}H n.m.r. spectra were recorded at 60Hz on Perkin-Elmer R24B or Varian EM360 spectrometers, at 100 MHz on a Jeol PS100 spectrometer or at 400 MHz using the SERC facility at Warwick University. In every case tetramethylsilane was used as an internal standard. Mass spectra and high resolution accurate mass measurements were determined on a VG7070E instrument with a VG200 data system.

TLC analyses were performed on Merck DC-Alufolien plates coated with Kieselgel $60F_{254}$, unless otherwise stated. Column chromatography was performed on short path columns packed with Merck 7747 silica gel, and the solvent was eluted under pressure provided by hand bellows.

All electrolyses were conducted with an H-type cell with an anolyte capacity of $150cm^3$. Unless stated otherwise, dry acetonitrile was used as the solvent and anhydrous sodium perchlorate (dried under reduced pressure at 125^{o} for twenty four hours) formed the supporting electrolyte, 2" sq. platinum gauze was used for both electrodes. The electrode potential was

monitored by a calomel electrode connected to the cell *via* an agar/potassium chloride conducting bridge and the current was provided by a Farnell stabilized power supply.

All cyclic voltammograms were recorded using a 'homebuilt' three electrode polarograph constructed by Dr. J.A. Wyatt. Voltammograms were displayed on either a Telequipment 261A oscilloscope or Hewlett Packard flat bed X-Y recorder (1 sec. pen response). Platinum wire or platinum bead microelectrodes were used as anodes for voltammetric measurements in a simple three electrode cell.

Acetonitrile was dried by distillation twice from phosphorus pentoxide (5.g cm^{-3}) and allowed to stand over $3A^{o}$ molecular sieves decanted onto fresh activated sieves (50g cm^{-3}) for a further 24 hours.

Tetrahydrofuran was dried by distillation from sodium/ benzophenone ketyl. Diethyl ether was dried by standing over sodium wire for 24 hours.

Dichloromethane was purified by distillation from calcium hydride. Dimethylformamide was dried by standing over $4A^{o}$ molecular sieves which had been activated by heating to 150^{o} overnight under reduced pressure.

6,7-Dimethoxyisoquinoline hydrochloride (26).

β-(3,4-Dimethoxyphenyl)ethylamine (25, 1.0g, 0.0056mol) was added to formaldehyde of[40% aqueous solution ($0.46cm^3$, 0.00616 mol)] heat was evolved and the turbid liquid was then heated on steam bath for thirty minutes. After this time excess water was removed and the residue treated with an excess of concentrated hydrochloric acid. The mixture was then evaporated to dryness on a steam bath and the crystalline product recrystallized from aqueous methanol (1.2g, 94.8%).

m.p. 252° lit.[17], m.p. 253°

I.R.

γ_{max} (cm^{-1}): 1660, 1595

^1H n.m.r.

δ(ppm, $CDCl_3$): 6.88, 6.81 (2s, 2H, aromatics), 4.3 (s, 2H, 1-H), 3.82(s, 6H, 2 x OCH_3), 3.5 (s, 2H, 3-H), 3.1 (s, 2H, 4-H).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 149.0, 148.3 (2s, C-6, C-7), 125.1 120.9 (2s, C-4a, C-8a), 112.8 (d, C-5), 110.7 (d, C-8), 56.8 (q, 4 x OCH_3), 45.2 (t, C-1), 42.9 (t, C-3), 25.2 (t, C-4).

Mass data

m/z (%) : 194 (M^+, 100), 193 (27), 180 (30).

3,4-Dimethoxybenzoyl chloride (27)

An ice cold solution of 3,4-dimethoxybenzoic acid (18.2g, 0.1 mol) and redistilled thionyl chloride ($40cm^3$) were heated under reflux in dry benzene ($100cm^3$) for 1.5 hours. Removal of the solvent under reduced pressure, gave a white solid which was used immediately (20g, 97%).

m.p. 76^o lit.[19a], m.p. 76^o

N-(3,4-Dimethoxybenzoyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (28)

3,4-Dimethoxybenzoyl chloride (27, 3.6g, 0.018 mol) was added to a stirred solution of 3,4-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (26, 4.0g, 0.018 mol) in dry ether (50 cm^3).

Trimethylamine (5.5 g, 7.6 mol) was then added dropwise to the above solution and the mixture was left stirring for 48 hours. Then the mixture was washed with water (20 cm^3), and a small volume of 2N hydrochloric acid ($10cm^3$). The ether layer was separated and the aqueous solution was extracted with ether (2 x $25cm^3$). The combined organic layers were washed with water (2 x $25cm^3$), dried over magnesium sulphate, and evaporated under reduced pressure to yield a white crystalline solid which was chromatographed over silica using chloroform as eluant (3.8g, 59.1%).

m.p. $131 - 132^o$

U.V.

λ_{max} (nm): 204, 283

I.R.

γ_{max} (cm^{-1}): 1620 (C=O), 1610, 1590.

^1H n.m.r.

δ(ppm, $CDCl_3$): 7.1 - 6.8 (complex, 3H, aromatics), 6.62 - 6.55 (2s, 2H, aromatics), 4.7(br.s, 2H, 1-H), 3.9, 3.85, 3.83 (3s, 12H, 4 x OCH_3), 3.81 (t, 2H, 3-H, J = 6Hz), 2.88 (t, 2H, 4-H, J = 6Hz).

Mass data

m/z (%): 357 (M^+, 15), 342 (5), 192 (35), 165 (100).

Accurate mass measurement

Found: 357.1570 calculated for $C_{20}H_{23}NO_5$:
357.1576

N-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (24, n = 1).

A solution of N-(3,4-dimethoxybenzoyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (28, 3.0g, 0.0084 mol) in dry tetrahydro furan ($25cm^3$) was added dropwise to a slurry of lithium aluminium hydride (0.4g) in dry tetrahydrofuran ($100cm^3$) and the mixture was stirred at 0^o for 3 hours. The cooled suspension was poured into 30% sodium potassium tartarate solution ($50cm^3$) and the precipitate which formed was filtered off through a layer of celite. The filtrate was reduced in volume and extracted with ethyl acetate (3 x $50cm^3$). The combined extracts were dried over magnesium sulphate and evaporated to give colourless

prisms (2.2g, 76.6%).

m.p. 92° lit.[68,69] m.p. 93°

I.R.

$\gamma_{max}(cm^{-1})$: 1610, 1595.

^1H n.m.r.

δ(ppm, $CDCl_3$): 6.99 - 6.88 (2m, 3H,aromatics), 6.60, 6.5 (2m 2H, aromatics), 3.89, 3.85, 3.81, 3.80 (4s, 12H, 4 x OCH_3), 3.63 (s, 2H, 1-H), 3.55 (s, 2H, CH_2-Ar), 2.85 - 2.7 (complex, 4H, 3-H, 4-H).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 149.3, 148.0, 147.8, 147.5(4s, C-6, C-7, C-3, C-4), 131.2, 127.0, 126.4 (3s, C-1, C-8a, C-4a), 121.3 (d, C-6), 112.5 (d, C-8), 111.8, 111.2, 109.9 (3d, C-5, C-2, C-5), 65.0, 62.5 (2t, C-1, CH_2-Ar), 56.0 (q, 4 x OCH_3), 30.7, 28.8 (2t, C-3, C-4).

Mass data

m/z (%): 342 (M^+, 15), 192 (100), 164 (65), 151 (60).

Accurate mass measurement

Found: 342.1710 calculated for $C_{20}H_{25}NO_4$:

342.1714

Electrochemical oxidation of N-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (24, n = 1)

The isoquinoline (24, n = 1, 1.5g, 0.00438 mol) and tetrabutylammonium-tetrafluoroborate (2.0g) in dry acetonitrile ($250cm^3$) was electrolysed at an anode potential of +1.1 volts (vs. SCE), using platinum gauze electrodes. After all the starting material had been oxidised (6 hours), the anolyte was separated, water ($10cm^3$) was added and the mixture was evaporated to near dryness. The dark residue was dissolved in chloroform ($55\ cm^3$), washed with water ($2 \times 20cm^3$) and finally dried over magnesium sulphate. Removal of the solvent by evaporation left a brown oil which was chromatographed over silica using 5% ethanol in 60 - 80^o petroleum ether as the eluant.

The following products were obtained in order of elution:

a - 3,4-dimethoxybenzaldehyde (36) isolated as an oil (^{0}.15g, 10%)

b - 3,4-dimethoxybenzoic acid (37, 0.12g, 8%)

c - 3,4-dihydro-6,7-dimethoxyisoquinoline (34, 0.24g, 16%).

Mass data

m/z (%): 191 (M^+), 189 (100).

The product was shown to be identical with an authentic sample prepared by the method of Späth and Polgar[25], by the usual spectroscopic and chromatographic techniques.

Methyl (3,4-dimethoxyphenyl)acetate (30)

3,4-Dimethoxyphenylacetic acid (29, 39.2g, 0.2mol) was dissolved in warm Analar methanol ($25cm^3$) and to it was added concentrated sulphuric acid ($5cm^3$). The mixture was heated under reflux for 2 hours. The cooled solution was added to water ($200cm^3$), basified with 2N ammonium hydroxide solution and extracted with ether ($3 \times 50cm^3$). The combined organic phases were washed with water ($50cm^3$), and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure, followed by vacuum distillation of the residue, gave the ester (30) as a colourless oil (37g, 88%).

b.p. 190 - 192°/0.7mm Hg) lit.[24], b.p. 192°/0.7mm Hg

U.V.

λ_{max}(nm): 210, 234, 284.

I.R.

$\gamma_{max}(cm^{-1})$: 1735 (C=O)

^{1}H n.m.r

δ(ppm, $CDCl_3$): 6.83 (complex, 3H, aromatics), 3.86 (s, 6H, 2 x OCH_3), 3.66 (s, 3H, $-OCH_3$), 3.56 (s, 2H, $CH_2-C(=O)-$).

Mass data

m/z (%): 210 (M^+, 30), 151 (100).

2-(3,4-Dimethoxyphenyl)ethanol (31).

A solution of methyl 3,4-dimethoxyphenyl acetate (30, 30.0g, 0.14 mol) in dry ether ($120cm^3$) was added dropwise to a slurry of lithium aluminium hydride (6.0g) in dry ether ($300cm^3$). The mixture was heated under reflux for one hour, cooled and excess reagent then decomposed by the cautious addition of water. The inorganic salts which separated out, were removed by filtration and washed with ether, finally, the filtrate was dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure left an oil which gave a pure white solid on standing (24.7g, 97%).

m.p. = 43 - 44° lit.[24], m.p. 44°

U.V.

λ_{max}(nm): 208, 231, 283.

I.R.

$\gamma_{max}(cm^{-1})$: 3300 (O-H)

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 6.70 (complex, 3H, aromatics), 3.82 (s, 3H, $OC\underline{H}_3$), 3.79 (s, 3H, $OC\underline{H}_3$), 3.76 (t, 2H, $C\underline{H}_2$-CH_2, $\underline{J}$ = 6Hz), 2.76 (t, 2H, CH_2-$C\underline{H}_2$, $\underline{J}$ = 6Hz), 1.88 (s, 1H, OH, removed by deuteration).

Mass data

m/z (%): 182 (M^+, 35), 165, 151 (100), 123.

2-(3,4-Dimethoxyphenyl)bromoethane (32)

2-(3,4-Dimethoxyphenyl)ethanol (31, 15.0g, 0.08 mol) was dissolved in dry ether (900 cm^3) and to it was added freshly distilled phosphorus tribromide (15cm^3) at 0^o. The mixture was allowed to stand overnight at room temperature, then washed with cold water (100cm^3) and finally with saturated aqueous sodium bicarbonate (100cm^3). It was then dried over anhydrous sodium sulphate and removal of the solvent under reduced pressure gave an oil which solidified on standing and which was crystallised as colourless rods from ethanol (9.6g, 49%).

m.p. 51^o lit.[21], m.p. 51^o

U.V.

λ_{max}(nm): 211, 236, 284.

I.R.

γ_{max}(cm^{-1}): 1135 (aromatic ether).

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 6.8 - 7.0 (complex, 3H, aromatics), 3.88 (s, 6H, 2 x OCH_3), 3.6 - 2.8 (complex, 4H, $-CH_2\ CH_2-$)

Mass data

m/z (%): 246/244 (M^+, 55), 231/229, 165, 151 (100)

6,7-Dimethoxy-3,4-dihydroisoquinoline (34)

(a) To an ice-cooled, stirred solution of 2-(3,4-dimethoxyphenyl) ethylamine (25, 9.58g, 0.052 mol) in 98% formic acid ($13cm^3$) under an atmosphere of nitrogen, was added acetic anhydride ($16cm^3$) drop by drop. The mixture was heated at 40^o for 3 hours and then cooled and diluted with water ($25cm^3$) and basified with 2N of ammonium hydroxide solution. The solution was extracted with dichloromethane (3 x $15cm^3$) and the combined organic layers were washed with 2M hydrochloric acid (2 x $15cm^3$) and dried over magnesium sulphate. Evaporation of the solvent left a yellow oil (7.2g, 76%).

m.p. and mixed m.p. $40 - 41^o$ lit.[25], m.p. $40 - 42^o$

(b) This amide (33, 20.0g, 0.097 mol) in dry benzene ($20cm^3$) was added dropwise to cool stirred solution of phosphorus pentachloride in dry benzene ($150cm^3$). The mixture was stirred at room temperature for 48 hours, then water ($200cm^3$) was added and the organic layer was separated and extracted with 2M hydrochloric acid (3 x $25cm^3$). The combined aqueous layers were basified with 2M ammonium hydroxide and extracted with dichloromethane (3 x $25cm^3$). These combined extracts were dried over magnesium sulphate and evaporated to give a yellow oil (14.4g, 72%).

m.p. and mixed m.p. $106 - 107^o$ lit.[25,70,71], m.p. $106 - 107^o$

N-(3,4-Dimethoxyphenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (24, n = 2).

(a) 2-(3,4-Dimethoxy)ethylbromide (32, 4.0g, 0.016 mol) and 3,4-dimethoxy-1,2-dihydroisoquinoline (34, 4.0g, 0.02 mol) were heated on a steam bath for 3 hours, after this time, the reaction mixture set to yield a crystalline mass which was recrystallised from ethanol to give the corresponding isoquinolinium salt as a yellow solid (7.2g, 75%).
m.p. 209 - 210° lit.[21], m.p. 210 - 211°

(b) This quarternary bromide (35, 0.13g, 0.00033 mol) was stirred for 4 hours with sodium borohydride (0.2g) in ethanol (50 cm^3), the solution was treated with 2M hydrochloric acid (2 x 25cm^3) then with 2M ammonium hydroxide (2 x 30 cm^3), and finally extracted with dichloromethane (3 x 25cm^3). The combined organic layers were washed with water (100cm^3) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a yellow solid which was chromatographed over silica using 5% ethanol in dichloromethane as eluant (0.09g, 84%).
m.p. 113 - 114° lit.[20], m.p. 113 - 114°

U.V.

λ_{max}(nm): 210, 230, 283, 286

I.R.

γ_{max}(cm^{-1}): 1610, 1595

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 6.8 (s, 3H, aromatics), 6.5, 6.6 (2s, 2H, aromatics), 4.1 (s, 2H, 1-H), 3.84 (s, 12H, 4 x OCH_3), 3.4 - 3.1

(complex, 8H, $\underline{CH}_2 - \underline{CH}_2$-Ar, 3-H, 4-H).

Mass data

m/z (%): 357 (M^+, 16), 206 (100).

Anodic oxidation of 2-(3,4-dimethoxyphenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (24, n = 2).

The substrate (24, n = 2, 0.83g,0.0023 mol) was electrolysed in dry acetonitrile using sodium perchlorate (0.2M) as the supporting electrolyte. The anode potential was maintained at +1.1 volts and the current at 100mA over a period of 1.5 hours. After this time the electrolysis was stopped, the anolyte was separated and water ($25cm^3$) was added. The mixture was evaporated to near dryness and then it was extracted with dichloromethane (2 x $25cm^3$). The combined extracts were washed with water (2 x $25cm^3$), dried over magnesium sulphate and evaporated to yield a brown oil which was chromatographed over silica using 5% ethanol in 60 - 80^o petroleum ether as eluent. The following products were obtained in order of elution:

(a) 3,4-dimethoxybenzaldehyde (36, 0.27g, 15%)

(b) 3,4-dimethoxybenzoic acid (37, 0.07g, 4%)

(c) 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium perchlorate (39) which was not isolated as such but was converted into 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline, by reduction with sodium borohydride in aqueous acetonitrile/ethanol solution. After treatment with warm dilute hydrochloric acid and basification, removal the solvents gave the tetrahydro-

isoquinoline as a pale brown oil (0.24g, 18%).

This compound was authenticated by comparison with a sample of 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline prepared from 3,4-dihydro-6,7-dimethoxyisoquinoline (34) by N-methylation with methyl iodide and reduction of the product with sodium borohydride. This product was also obtained initially as an oil, but it slowly crystallised on standing.
m.p. 82 - 83° lit.[27], m.p. 83 - 84°

3-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (41)[28]

(a) A solution of papavarine methiodide (49, 2.0g, 0.004 mol) in dry tetrahydrofuran (200cm^3) was added dropwise to a slurry of lithium aluminium hydride (1.19g) in dry tetrahydrofuran (300cm^3). The mixture was heated under reflux for 3 hours and then cooled. A solution of potassium sodium tertarate (20%, 200cm^3) was added. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 25cm^3). The combined organic layers were washed with water (2 x 25cm^3) and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave an orange oil which could not be purified further.

(b) The orange oil was dissolved in 2M hydrochloric acid (100cm^3) and heated at 100° for 5 hours. The cooled solution was basified with 2M sodium bicarbonate to pH 8.8 and extracted with chloroform (2 x 25cm^3). The extracts were washed with water and dried over magnesium sulphate. Evaporation of the solvent left a yellow gum which was dissolved in ethanol and treated with sodium borohydride (0.5g) The mixture was left stirring at room temperature for 48 hours and

extracted with dichloromethane (3 x 25cm^3). The combined organic phases were washed with water and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a yellow oil which was chromatographed over silica using 50% ethyl acetate in 60 - 80^o petroleum ether as eluant to give white solid (1.39g, 70%).

U.V.

λ_{max}(nm): 235, 286

I.R.

γ_{max}(cm^{-1}): 1600, 1595

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 6.6(complex, 3H, aromatics), 6.51 (s, 2H aromatics), 3.9 (s, 2H, 1-H), 3.8 (s, 12H, 4 x OCH_3) 2.8 - 3.2 (complex, 5H 3-H, 4-H, CH_2-Ar), 2.6 (s, 3H, CH_3).

Mass data

m/z(%): 356 (M^+, 45), 206 (100)

Electrolysis of 3-(3,4-dimetheoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (41).

The substrate (41, 2.0g, 0.0056 mol) was electrolysed in dry acetonitrile (250cm^3) using tetra-n-butylammoniumtetrafluoroborate (2.0g) as supporting electrolyte. Platinum gauze electrodes were used and a current of 100mA was passed through the cell for a period

of 6 hours. After this time, the anolyte was separated, water ($20cm^3$) was added and the mixture evaporated near dryness. The dark residue was dissolved in chloroform ($100cm^3$), washed with water ($50cm^3$) and dried using magnesium sulphate and the solvent removed by evaporation under reduced pressure. The resultant oil was chromatographed over silica using 25% ethyl acetate in 60 - 80° petroleum ether as eluant to yield the following compounds.

(a) 5,6,7,8-Tetrahydro-2,10,11-trimethoxy-6-methyl-7,12b-methano-dibenzene[c,e]azocine-3-one (42) as a white solid (1.3g, 68%).
m.p. and mixed m.p. 168 - 170° lit.[31], 168.5 - 170°

U.V.

λ_{max}(nm): 232, 290

I.R.

$\gamma_{max}(cm^{-1})$: 1660, 1640, 1620.

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 6.77 (s, 1H, 12-H), 6.50 (s,1H, 9-H), 6.15 (s,1H, 5-H), 5.94 (s,1H, 8-H), 3.88, 3.77, 3.72 (3s, 9H, 3 x $OC\underline{H}_3$), 3.35 (br.s, 2H, 2-H), 3.20 (dd, 1H, 1A-H, $\underline{J}_1$ = 18Hz, $\underline{J}_2$ = 6.5Hz), 3.11 (s, 2H, 4-H), 2.97 (dd, 1H, 1B-H, $\underline{J}_1$ = 18Hz, $\underline{J}_2$ < 1Hz), 2.54 (s, 3H, $C\underline{H}_3$), 2.26 (dd, 1H, 13A-H, $\underline{J}_1$ = 12.5Hz, $\underline{J}_2$ = 1.8Hz), 2.06 (ddd, 1H, 13B-H, $\underline{J}_1$ = 12.5Hz, $\underline{J}_2$ = 1.5Hz, $\underline{J}_3$ = 4.0Hz).

Mass data

m/z, (%): 341 (M^+, 66), 206, (19), 192 (27), 94 (100).

(b) 5,6,7,8-Tetrahydro-8-hydroxy-2,10,11-trimethoxy-6-methyl-7,12b-methanodiben[c,e]azocine-6-one (43)as white crystals (0.1g, 5%).

m.p. 187 - 188° lit.[31], m.p. = 188 - 189°

U.V.

λ_{max}(nm): 260, 290

I.R.

γ_{max}(cm^{-1}): 3400 - 3300 (OH), 1680, 1620, 1610

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 7.01 (s, 1H, 12-H), 6.47 (s, 1H, 9-H), 6.07 (s, 1H, 5-H), 5.93 (s, 1H, 8-H), 4.85 (br.s, 1H, 1-H) 3.87, 3.74, 3.69 (3s, 9H, 3 x OCH_3), 3.24 (br.s, 2H, 2-H), 3.03 (d, 1H, 4A-H, J = 14Hz), 2.96 (d, 1H, 4B-H, J = 14Hz), 2.54 (s, 3H, $-CH_3$), 2.54 (dd, 1H, 13A-H , J_1 = 12.5Hz, J_2 = 1.8Hz), 1.85 (dd, 1H, 13B-H, J_1 = 12.5Hz, J_2 = 1.8Hz).

Mass data

m/z (%): 357 (M^+, 48), 355 (14), 354 (10), 206 (100).

4-Ethoxy-3-methoxybenzaldehyde (61)

4-Hydroxy-3-methoxybenzaldehyde (60, 2.5g, 0.082 mol), ethylbromide (9 cm^3), potassium hydroxide (9.18g) and ethanol (45cm^3) were heated at reflux for 6 hours. The cooled mixture was then filtered and the solid washed with water and crystallised from methanol. The filtrate was cooled to 0° and the crystals which separated were collected and recrystallised from methanol to yield colourless needles (2.7g, 90%).

m.p. 63 - 64° lit.[40], m.p. 64 - 65°

U.V.

λ_{max}(nm): 230, 295, 310

I.R.

γ_{max}(cm^{-1}): 1670, 1590

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 9.8 (s, 1H, $\underset{\underset{O}{\|}}{C}-H$), 7.4 - 6.8 (complex, 3H, aromatics), 4.2 (q, 2H, CH_2CH_3, J = 6Hz), 3.9 (s, 3H, OCH_3), 1.55 (t, 3H, CH_3CH_2, J = 6Hz).

Mass data

m/z (%): 180 (M^+, 62), 151 (100).

Tetraethyldimethylaminomethylenediphosphonate (66)

Dimethylformamide acetal (2.2g, 0.0168 mol) and diethyl phosphite (4.64g,0.033 mol) were heated to 80 - 90°C for 2 - 3 hours under a nitrogen atmosphere. The cooled product was distilled under high vacuum to give a colourless liquid (5.0g, 93%).

b.p. 140°/0.55mmHg lit.[45], b.p. 114 - 115°/0.03mm Hg

U.V.

λ_{max}(nm): 203

I.R.

γ_{max}(cm^{-1}): 1450, 1415

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 4.3 - 3.8 (multiplet, 8H, 4 x $\underline{CH}_2$-CH_3, $\underline{J}$ = 4Hz), 3.2 (t, 1H, =CH, $\underline{J}$= 25Hz, 2.6 (t, 6H, $N(\underline{CH}_3)_2$, $\underline{J}$ = 1.5Hz), 1.4 (t, 12H, 4 x $\underline{CH}_3$-CH_2, $\underline{J}$ = 7Hz).

2-(4-Ethoxy-3-methoxyphenyl)acetic acid (62)

(a) Tetraethyldimethylaminomethylenediphosphonate (66, 2.0g, 0.007mol) in dry dioxane (5 cm^3) was added dropwise at room temperature to a suspension of sodium hydride (0.16g, 0.01 mol) in dry dioxane (15cm^3). The mixture was stirred for 2 hours and 4-ethoxy-3-methoxybenzaldehyde (61, 1.0g, 0.0056 mol) in dry dioxane (5 cm^3) was added dropwise. The reaction mixture was heated to 80^o for 2 hours, and allowed to cool, it was then poured into cold water (100 cm^3), which was extracted with ether (3 x 25 cm^3), the organic layers were dried over sodium sulphate and evaporated to give an oily compound (2.5g, 98%).

(b) The phosphonate ester (2.0g, 0.0053 mol) in concentrated hydrochloric acid was heated for 20 minutes. The cooled solution was added to the water (50 cm^3) and extracted with chloroform (2 x 25 cm^3). The combined organic extracts were basified with 20% of sodium carbonate and the aqueous layer was removed and acidified with 2N of hydrochloric acid. Extraction with chloroform (2 x 25 cm^3) and removal of the solvent under reduced pressure give a white solid (0.4g, 36%).

m.p. 156 - 157^o lit.[72], m.p. 158^o

U.V.

λ_{max}(nm): 230, 280

I.R.

γ_{max}(cm^{-1}): 1690, 1610, 1595

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 6.78 (s, 3H, aromatics), 4.21 (q, 2H, $\underline{CH}_2$-CH_3, $\underline{J}$ = 7Hz), 3.85 (s, 3H, -O$\underline{CH}_3$), 3.55 (s, 2H, $\underline{CH}_2C(=O)$-) 1.4 (t, 3H, $\underline{CH}_3$-CH_2, $\underline{J}$ = 7Hz).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 177.8(s, C=O), 149.3, 147.6 (2s, C-3, C-4), 125.8 (s, C-1), 121.6 (d, C-6), 112.9 (d, C-2, C-5), 64.4 (t, $\underline{CH}_2$-C(=O)-), 55.9 (q, O$\underline{CH}_3$), 40.6 (t, $\underline{CH}_2$-CH_3), 14.78 (q, $\underline{CH}_3$-CH_2).

Mass data

m/z (%): 210 (M^+, 89), 182 (30), 165 (14), 137 (100).

Found: C, 62.6; H, 6.75. Calculated for $C_{11}H_{14}O_4$:
C, 62.8; H, 6.7%

7-Ethoxy-6-methoxyisochroman-3-one (63)

2-(4-Ethoxy-3-methoxyphenyl) acetic acid (62, 1.0g, 0.004 mol) in glacial acetic acid (3 cm^3) was heated to 60° and concentrated hydrochloric acid (1 cm^3) was added. This was followed by the addition of 37% formalin solution (1 cm^3) and the yellow solution was heated at 90° for a further 1.25 hours. After cooling, the dark solution was poured into cold water (10 cm^3) and extracted with chloroform (4 x 20 cm^3). The combined organic extracts were

washed with saturated sodium bicarbonate solution until neutral, then with water (2 x 20 cm^3) and finally, they were dried over magnesium sulphate. Evaporation of the solvent give a white solid which was recrystallised from ethanol to form white needles (0.86g, 82%)

m.p. 106 - 107°

U.V.

λ_{max}(nm): 205, 285

I.R.

$\gamma_{max}(cm^{-1})$: 1740 (C=O), 1620

^1H n.m.r.

δ(ppm, $CDCl_3$): 6.66, 6.62 (2s, 2H, aromatics), 5.15 (s, 2H, 1-H), 4.01 (q, 2H, $C\underline{H}_2CH_3$, $\underline{J}$ = 7.5Hz), 3.80 (s, 3H, $OC\underline{H}_3$), 3.55 (s, 2H, 4-H), 1.4 (t, 3H, $C\underline{H}_3-CH_2$, $\underline{J}$ = 7.5Hz).

^{13}C n.m.r.

δ(ppm , $CDCl_3$): 170.7 (C=O), 148.2, 147.7 (2s, C-6, C-7), 124.6, 123.0(2s, C-4a, C-8a), 110.6, 109.8 (2d, C-8, C-5), 70.4 (t, C-1), 64.8 (t, $C\underline{H}_2-CH_3$), 56 (q, $OC\underline{H}_3$) 35.6 (t, C-4), 14.7 (q, $C\underline{H}_3-CH_2$).

Mass data

m/z (%): 222 (M^+, 100), 194 (10), 178 (20), 150 (82), 135 (25), 121 (22).

Found: C, 64.7; H, 6.30 $C_{12}H_{14}O_4$ requires:

C 64.8; H, 6.35%

4-(3,4-Dimethoxybenzylidene)-7-ethoxy-6-methoxyisochroman-3-one (64).

7-Ethoxy-6-methoxyisochroman-3-one (63, 0.5g, 0.002 mol), 3,4-dimethoxybenzaldehyde (36, 0.4g, 0.002 mol) and pyrrolidine (0.1 cm^3) were heated under a dry nitrogen atmosphere at 140° for 2.5 hours. The cool gum was treated with 10% acetic acid in ethanol (5 cm^3), the gum-solid which remained was collected and chromatographed over silica using chloroform as eluant to give yellow oil which crystallised and recrystallised from methanol to give pale yellow prisms (0.5g, 60%).

m.p. 168 - 170°C

U.V.

λ_{max}(nm): 245, 375

I.R.

γ_{max}(cm^{-1}): 1710 (C=O), 1602, 1598

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 7.62 (s, 1H, =CHAr), 7.10 - 6.68 (m, 5H, aromatics), 5.19 (s, 2H, 1-H), 4.02, (q, 2H, $-O\underline{CH_2}-CH_3$, J = 7.5Hz), 3.85, 3.70, 3.50 (3s, 9H, 3 x $O\underline{CH_3}$), 1.45 (t, 3H, $\underline{CH_3}CH_2$, J = 7.5Hz).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 164 (s, C=O), 150.4, 150.2, 148.6, 148.5 (4s, C-'3, C-'4, C-6, C-7), 136.4, 113.2, 112.3, 111.0, 109.1, 108.8 (6s, C-8, C-'2, C-'5, C-'6, C-5, $\underline{CH}$=), 128.2, 124.2, 123.8 (3s, C-8a, C-'1, C-4a), 69.0 (t, $\underline{CH_2}$ CH_3), 64.5 (t, C-1), 55 (q, 3 x $O\underline{CH_3}$), 14.7 (q, $\underline{CH_3}$ CH_2)

Mass data

m/z (%): 370 (M^+, 100), 341 (15).

Found: C, 68.0; H, 5.9 $C_{21}H_{22}O_6$ requires:

C, 68.1; H, 6.0%

4-(3,4-Dimethoxybenzyl)-7-ethoxy-6-methoxyisochroman-3-one (65)

4-(3,4-Dimethoxybenzylidene)-7-ethoxy-6-methoxyisochroman-3-one (64, 2.0g, 0.0054 mol) in ethyl acetate (150 cm^3) was hydrogenated at 60 lb cm^2 over a platinum oxide catalyst (0.17 g). After 10 hours, the solution was filtered through Kieselguhr followed by evaporation of the solvent, left a light brown oil which slowly crystallized. Recrystallisation from ethanol yielded colourless solid (0.95 g,47%). m.p. 113 - 115°.

U.V.

λ_{max}(nm): 235, 283

I.R.

γ_{max}(cm^{-1}): 1740, 1615

^1H n.m.r.

δ(ppm, $CDCl_3$): 6.80 - 6.35 (m, 5H, aromatics), 4.75 (s, 2H, 1-H), 4.12 (q, 2H, OCH_2 CH_3, J = 7Hz), 3.80, 3.68, 3.60 (3s, 9H, 3 x OCH_3), Ca. 3.7 (t, 1H, 4-H, J = 15Hz), 3.20 (d, 2H, CH_2-Ar, J = 15Hz), 1.51 (t, 3H, OCH_2 CH_3, J= 7Hz).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 172.4 (s, C=O), 148.65, 148.16, 147.7, 147.5 (4s, C-'3, C-'4, C-6, C-7), 129.5, 125.4, 121.6 (3s, C-8a, C-'1, C-4a), 123.1, 112.5, 111.1, 110.3, 108.5, (5d, C-8, C-'2, C-'5, C-'6, C-5), 69.5 (t, $\underline{C}H_2$ CH_3), 64.5 (t, CH_2-Ar), 56.0, 55.9, 55.7 (3q, 3 x $O\underline{C}H_3$), 47.0 (d, C-4), 38.7 (t, C-1), 14.7 (q, $\underline{C}H_3$ CH_2).

Mass data

m/z (%): 372 (M^+, 5), 151 (100).

Found: C, 67.6; H, 6.3 $C_{21}H_{24}O_6$ requires:
C, 67.7; H, 6.5%.

7a,8-Dihydro-3,10,11-trimethoxy-2H-phenanthro[9,8a-b]furan-2,7(5H)-dione (57)

4-(3,4-Dimethoxybenzyl)-7-ethoxy-6-methoxyisochroman-3-one (65, 0.7g, 0.0018 mol) in 0.2M anhydrous sodium perchlorate in dry acetonitrile (250 cm^3), was electrolysed at an anode potential of 1.1 volts (vs SCE) at room temperature using a platinum gauze anode and a mercury pool cathode. After all the starting material has been oxidised (≃ 1 hour), the anolyte was separated, water (15 cm^3) was added and the mixture evaporated near dryness. The light yellow oil was dissolved in chloroform (100cm^3), and the solution was washed with water (50 cm^3) and then dried over magnesium sulphate. After evaporation, the resultant oil was crystallized from diethyl ether and recrystallized from ethanol to give white needles (0.41 g, 67%).

m.p. 256 - 257° lit.[12], m.p. 256 - 257°

U.V.

λ_{max}(nm): 265, 290, 360

I.R.

γ_{max}(cm^{-1}): 1760, 1660, 1650, 1610

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 6.98 (s, 1H, 12-H), 6.79 (s, 1H, 9-H), 6.51 (s, 1H, 1-H), 6.00 (s, 1H, 4-H), 4.24, 3.98 (AB, 2H, 5-H , J = 12.5Hz), 3.94 3.92 (2s, 6H, 2 x OCH_3), 3.76 (s, 3H, 3-OCH_3),3.20 - 3.00 (m, 3H, 7a-H, 8-H).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 180.2 (s, C=O), 177.7 (s, C-7), 155.2, 151.6, 151.0, 149.0(4s, C-3, C-12b, C-11, C-10), 128.0 (s, C-8a), 126.0 (s, C-4a), 124.2 (d, C-4), 116.7 (d, C-9), 111.2 (d, C-12), 108.7 (d, C-1), 77.6 (t, C-5), 47.0 (s, C-12a), 43.1 (d, C-7a), 28.9 (t, C-8).

Mass data

m/z (%): 324 (M^+,100) , 284 (28), 266 (15), 253 (58)

Electro-oxidation of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (50)

(i) In acetonitrile-methanol

The substrate[2] (50, 1.0g, 0.0028 mol) was electrolysed in 0.1M anhydrous sodium perchlorate in acetonitrile-methanol (1:1) at an anode potential of +1.15 volts (vs SCE) using platinum gauze electrodes. After the passage of two Faradays of electricity per mole of substrate, the anolyte was added to water (20 cm^3) and the mixture evaporated to near dryness. The dark residue was dissolved in chloroform (40 cm^3), washed with water (30cm^3) and dried over magnesium sulphate. After evaporation, the resultant

oil was chromatographed over silica using 40% ethyl acetate in ether as the eluant. The following products were obtained in order of eluant.

(a) 7a-8-Dihydro-3,10,11-trimethoxy-2H-phenanthro-[9, 8a-b]furan-2,7(5H)-dione (57, 0.078g, 8%).
m.p. 256 - 257° lit.[12], m.p. 256 - 275°

(b) 4,6,7-Trimethoxy-4-(3,4-dimethoxybenzyl)isochroman-3-one (71, 0.27g, 25%).
m.p. 137°

I.R.

$\gamma_{max}(cm^{-1})$: 1735

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 6.95 (s, 1H, 8-H), 6.80 (d, 1H, '5-H, J = 8Hz), 6.44 (dd, 1H, '6-H, J = 8Hz, J = 2Hz), 6.42 (s, 1H, 5-H), 6.14 (d, 1H, '2-H, J = 2Hz), 4.93, 3.80 (AM, 2H, 1-H, J = 15Hz), 3.92, 3.88, 3.84, 3.60 (4s, 12H, 4 x $O\underline{CH}_3$), 3.40, 3.04 (AB, 2H, $\underline{CH}_2$-Ar, J = 7Hz) 3.22 (s, 3H, 4-$O\underline{CH}_3$).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 170.9 (s, C=O), 150.0, 149.5, 148.4, 148.3, (4s, C-7, C-6, C-'3, C-'4), 125.8 (s, C-'1), 125.1 (d, C-'6), 124.6 (d, C-8), 122.8 (s, C-8a), 113.5 (s, C-4a), 110.8, 108.2, 105.6 (3d, C-5, C-'5, C-'2), 80.7 (s, C-4), 69.1 (t, C-1), 56.3, 56.1, 55.8 (q, 5 x $O\underline{CH}_3$), 48.8 (t, $C\underline{H}_2Ar$).

Mass data

m/z (%): 388 (M^+, 4), 237 (71), 151 (100)

Found: C, 64.85; H, 6.1 $C_{21}H_{24}O_7$ requires:

C, 64.9; H, 6.2%

(ii) In acetonitrile-pyridine

The substrate[2] (50, 1.0g, 0.0028 mol) was dissolved in 0.1M sodium perchlorate in dry acetonitrile-pyridine (10:1) and electrolysed at an anode potential of +0.9 - 1.0 volts (vs SCE) using platinum gauze electrodes. After the passage of two Faradays of electricity per mole of substrate, the electolysis was stopped and the anolyte was added to water (40 cm^3 9). The mixture was then evaporated to near dryness, the residue was dissolved in chloroform (40 cm^3), washed with water (50 cm^3) and dried over magnesium sulphate and evaporated to give a brown oil, which was chromatographed over silica using 3% methanol in dichloromethane as eluant. The following products were obtained in order of elution:

(a) 3,4-Dimethoxybenzaldehyde (36, 0.1g, 10%).

m.p. and mixed m.p. 42 - 45° (comparison with commercially available sample).

(b) 4-Hydroxy-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isochroman-3-one (79, 0.25g, 25%)

m.p. 148 - 150°

U.V.

λ_{max}(nm): 225, 276

I.R.

γ_{max}(cm^{-1}): 3490(OH), 1740, 1615, 1600

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 6.98 (s, 1H, 8-H), 6.65 (d, 1H, '5-H, J = 8Hz), 6.45 (s, 1H, 5-H), 6.43 (dd, 1H, '6-H, J = 8Hz, J = 2Hz), 6.26 (d, 1H, '2-H, J = 2Hz), 4.90 (AM, 2H, 1-H, J = 20Hz), 3.82 (s, 9H, 3 x OCH_3), 3.64 (s, 3H, OCH_3), 3.20 (s, 2H, CH_2Ar).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 177.2 (s, C-3), 148.6, 148.4, 147.8, 147.6 (4s, C-'3, C-'4, C-6, C-7), 126.3 (s, C-8a), 122.5 (d, C-'6), 121.7 (s, C-4a), 113.7, 111.0 108.2, 106.5 (4d, C-'2, C-5, C-'5, C-8), 73.7 (s, C-4), 69.9 (t, C-1), 56.1, 55.8 (2q, 4 x OCH_3), 47.2 (t, $ArCH_2$).

Mass data

m/z (%): 357 (M^+, 11), 223 (23), 151 (100).

Found: C, 64.1; H, 6.0 $C_{20}H_{22}O_7$ requires:
C, 64.2; H, 5.9%

(iii) In acetonitrile-water

The lactone[2] (50, 1.0g, 0.0028 mol) was electrolysed in water acetonitrile-water (10:1) using sodium perchlorate (0.2M) as supporting electrolyte at an anode potential of + 1.1 volts over a period of four hours. After this time the electrolysis was stopped and the anolyte was added to water (200 cm^3), the mixture was then evaporated to near dryness, the residue was dissolved in chloroform (50 cm^3), washed with water (30 cm^3), dried over magnesium sulphate and evaporated to give a brown gum which was chromatographed over silica using 10% ethyl acetate in dichloromethane as eluant. The

following products were obtained in order of elution:

(a) 7a-8-Dihydro-3,10,11-trimethoxy-2H-phenanthro[9,8a-b]furan-2,7(5H)-dione (57, 0.08g, 8%).

(b) 3,4-Dimethoxybenzaldehyde (36, 0.06g, 6%).

(c) 5,6-Dimethoxyisobenzofurane-1-(3H)-one (73, 0.12g, 22%).

m.p. 154 - 156° lit.[47], m.p. 154 - 156°

U.V.

λ_{max}(nm): 250, 285, 295

I.R.

γ_{max}(cm^{-1}): 1756, 1600

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 7.28 (s, 1H, 7-H), 6.92 (s, 1H, 4-H), 5.20 (s, 2H, 1-H), 3.94, 3.85 (2s, 3H, 2 x $O\underline{CH_3}$).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 171.5 (s, C=O), 155.0, 150.5 (2s, C-5, C-6), 141.2 141.1 (2s, C-3a, C-7a), 106.2, 103.6 (2d, C-4, C-7), 69.2 (t, C-3), 56.4, 56.3 (2q, 2 x $O\underline{CH_3}$).

Mass data

m/z (%): 194 (M^+, 10), 165 (100).

Found: C, 61.7; H, 5.4 Calculated for $C_{10}H_{10}O_4$:
C, 61.85; H, 5.2%

Electro-oxidation of 6,7-dimethoxyisochroman-3-one (91)

The substrate[36] (91, 1.0g, 0.0048 mol) was electrolysed in 0.1M sodium perchlorate in acetonitrile-water (10:1), platinum gauze electrodes were used at a potential difference of + 1.1 volts (vs SCE) at a current 60mA for a period of five hours. After this time, the anolyte was separated, water (10 cm) was added and the mixture evaporated to near dryness. The dark residue was dissolved in chloroform (50 cm^3), washed with water (2 x 20 cm^3), and finally dried over magnesium sulphate. Removal of the solvent by evaporation left a brown gum, which was chromatographed over silica using 5% ethyl acetate in dichloromethane as eluant to obtain 5,6-dimethoxyisobenzofurane-1-(3H)-one (73, 0.61g, 65%) which was identical in every respect with a sample prepared by an alternative route[42] (see page 172).

6,7-Dimethoxyisobenzofurane-1-(3H)-one (73)

Formaldehyde [of 40% aqueous solution (230 cm^3)] was saturated with hydrogen chloride at 15 - 20°, before veratric acid (32g, 0.176 mol) was added. The mixture was then heated to 60 - 70° for 7 hours during which time a slow stream of hydrogen chloride gas was introduced. The mixture was cooled and then reduced in volume. Water (100 cm^3) was added to the residue and the mixture was neutralized with 2M ammonium hydroxide solution. A solid which formed and was filtered off, washed several times with water, dried and crystallised from methanol to give the title compound (22.4 g,

65.6%).

m.p. 154 - 155° lit.[47], m.p. 154 - 156°

All spectral data agree with those previously reported.

Electro-oxidation of 4,6,7-trimethoxy-4-(3,4-dimethoxybenzyl)iso-chroman-3-one (71)

The substrate (71, 1.0g, 0.0025 mol) was electrolysed in 0.1M sodium perchlorate in dry acetonitrile (250 cm^3) at an anode potential + 1.15 volts (vs SCE) using platinum gauze as electrodes. After the passage of two Faradays of electricity per mole of substrate, the anolyte was separated and was added to water (20 cm^3) and the mixture evaporated to near dryness. The dark residue was dissolved in chloroform (25 cm^3), washed with water and dried over magnesium sulphate. After the evaporation, the resultant oil was chromatographed over silica using ethyl acetate as eluant to give the product 7a,8-dihydro-3,7a,10,11-tetramethoxy-2H-phenanthro[9,8a-b] furan-2,7,8-trione (72, 0.67g, 67%).

m.p. 232° (dec.)

U.V.

λ_{max}(nm): 225, 296, 365

I.R.

$\gamma_{max}(cm^{-1})$: 1785, 1660, 1645, 1610.

^{1}H n.m.r.

δ(ppm, $CDCl_3$: 7.62 (s, 1H, 9-H), 7.26 (s, 1H, 12-H), 7.11 (s, 1H, 1-H), 6.08 (s, 1H, 4-H), 4.20 (s, 2H, 5-H), 4.03 (s, 3H, 11-OCH_3), 4.01 (s, 3H, 10-OCH_3), 3.81 (s, 3H, 3-OCH_3), 3.34 (s, 3H, 7a-OCH_3).

N.O.e experiment

Irrad. at δ4.01, enhancement at δ7.62 (7.2%) and 4.03 (16.3%); irrad. at δ4.03, enhancement at δ4.01 (15.7%) and 7.26 (5%); irrad. at δ7.26, enhancement at δ7.11 (5%); irrad. at δ3.81, enhancement at δ6.08 (6%) and 3.34 (10%).

Mass data

m/z (%): 386 (M^+, 58), 355 (46), 327 (100).

Found: C, 62.1; H, 4.6 $C_{20}H_{18}O_8$ requires:
C, 62.2; H, 4.7%

6-Methoxy-3-isochroman-3-one (82)

2-(3-Methoxyphenyl) acetic acid (81, 10g, 0.066 mol), glacial acetic acid (45 cm^3), concentrated hydrochloric acid (3 cm^3), 37% formalin solution (15 cm^3) was stirred at room temperature for 5 days. After cooling, the dark solution was poured into cold water (250cm^3) and extracted with chloroform (4 x 20 cm^3). The combined organic extracts were washed with saturated sodium bicarbonate solution until neutral, then with water (2 x 20 cm^3) and finally they were dried over magnesium sulphate. Evaporation of the solvent give a white solid which was recrystallised from ethanol to form white needles (5.1g, 43%).
m.p. 75 - 78° lit.[73], m.p. 75 - 78°

I.R.

$\gamma_{max}(cm^{-1})$: 1737 (C=O), 1618

^1H n.m.r.

δ(ppm, $CDCl_3$): 7.34 - 6.54 (m, 3H, aromatics), 5.20 (s, 2H, 1-H),

3.74 (s, 3H, OCH_3), 3.61 (s, 2H, 4-H).

Mass data

m/z (%): 178 (M^+, 90), 149 (25), 135 (15), 134 (100).

6-Methoxy-4-(3-methoxybenzylidene)isochroman-3-one (83)

6-Methoxyisochroman (82, 0.6g, 0.0034 mol), 3-methoxybenzaldehyde (0.52g, 0.0039 mol) and piperidine (0.1g) were heated at 140° under an atmosphere of nitrogen. After two hours, the mixture was allowed to cool and then it was treated with 40% acetic acid in methanol (15 cm^3). A yellow solid which formed was collected and purified by column chromatography over silica using chloroform as an eluant to give the title compound as yellow prisms (0.82g, 83%).
m.p. 140 - 141°.

U.V.

λ_{max}(nm): 245, 323.

I.R.

γ_{max}(cm^{-1}): 1720, 1610

^1H n.m.r.

δ(ppm, $CDCl_3$): 7.81 (s, 1H, =CHAr), 7.23 - 6.90 (m, 7H, aromatics), 5.28 (s, 2H, 1-H), 3.72, 3.52 (2s, 6H, 2 x OCH_3).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 168.4 (s, C=O), 152.8, 152.6 (2s, C-3, C-6), 138.7, 129.7, 126.3, 121.9, 115.7, 115.5, 114.6, 111.9 (8d, C-8, C-'2, C-'4, C-'5, C-5, C-'6, C-7, =CHAr), 135.7, 125.6, 125.0 (3s, C-'1, C-4a,

C-8a), 69.0 (t, C-1), 55.2 (2q, 2 x $O\underline{C}H_3$).

Mass data

m/z (%): 296 (M^+, 100), 251 (36), 237 (25), 177 (18).

Found: C, 72.8; H, 5.6 $C_{18}H_{16}O_4$ requires:
C, 73.0; H, 5.4%

6-Methoxy-4-(3-methoxybenzyl)isochroman-3-one (84).

6-Methoxy-4-(3-methoxybenzylidene)isochromanone (83, 0.6g, 0.002 mol) in ethylacetate (200 cm^3) was hydrogenated for 10 hours at atmospheric pressure over 10% palladium on charcoal (0.12g) as catalyst. The solution was filtered through Kieselguhr, and the solvent then evaporated to leave a colourless oil which slowly recrystallized (0.55g, 92%).

m.p. 79.5 - 81°

U.V.

λ_{max}(nm): 213, 285

I.R.

γ_{max}(cm^{-1}): 1722, 1595, 1585

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 7.15 - 6.97 (m, 3H, aromatics), 6.8 - 6.5 (m, 4H, aromatics), 5.10, 4.25 (2d, 2H, 1-H, J_{gem} = 12Hz), 3.90 (br, t, 1H, 4-H, J = 6Hz), 3.69 (s, 3H, 2 x $O\underline{C}H_3$), 3.11 - 3.90 (d, 2H, $\underline{C}H_2Ar$, J = 6Hz).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 172 (s, C=O), 159.6 (s, C-'3, C-6), 138.7, 135.2, 123.4 (3s, C-'1, C-4a, C-8a), 129.4, 125.5, 121.6, 111.7, 113.3, 112.8, 112.4, (7d, C-7, C-8, C-'2, C-'4, C-'5, C-5, C-'6), 69.3 (t, C-1), 55.3, 55.1 (2q, 2 x $O\underline{C}H_3$), 47.6 (d, C-4), 38.1 (t, $\underline{C}H_2Ar$).

Mass data

m/z (%): 298 (M^+, 15), 177 (85), 121 (100).

Found: C, 72.4; H, 6.2 $C_{18}H_{18}O_4$ requires:
C, 72.5; H, 6.1%

Anodic Oxidation of 6-methoxy-4-(3-methoxybenzyl)isochroman-3-one (84)

The substrate (84, 1.5g, 0.005 mol) was electrolysed in 0.1M solution of sodium perchlorate in acetonitrile/methanol (5:1). Platinum gauze electrodes were used and maintained at a potential difference of 1.2 volts (vs SCE). A current of 0.2A was passed through the cell for a period of 3.5 hours and after this time the anolyte was separated. Water (20 cm^3) was added and the mixture evaporated to near dryness. The residue was then dissolved in chloroform (40 cm^3) and washed with water (40 cm^3). The organic phase was dried over magnesium sulphate and the solvent evaporated to produce a brown oil which was purified by chromatography over silica using 20% ethyl acetate in 60 - 80° petroleum ether as eluant.

Two products were obtained in order of eluant:

(a) Methyl-2-formyl-5-methoxyphenyl-'3-methoxybenzyl acetate (87) as colourless oil (0.4g, 24%).

U.V.

λ_{max}(nm): 222, 237

I.R.

γ_{max}(cm^{-1}): 1730, 1680, 1595

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 9.96 (s, 1H, C<u>H</u>O), 7.80 (d, 1H, 3-H, <u>J</u> = 8.5Hz), 7.22 - 6.76 (m, 6H, aromatics), 5.16 (br.t, 1H, α-CH, <u>J</u> = 7Hz), 3.82, 3.75 (2s, 6H, 2 x O<u>CH</u>$_3$), 3.61 (s, 3H, <u>CH</u>$_3$C(=O)O), 3.50, 2.87 (dd, 2H, <u>CH</u>$_2$Ar, <u>J</u>= 16Hz, <u>J</u> = 7Hz).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 191.0 (s, <u>C</u>HO), 173.4 (s, <u>C</u>O$_2$CH$_3$), 166.0, 163.9, (2s, C-5, C-'3), 142.7, 139.2, (2s, C-1, C-'1), 137.0, 129.3, 121.5, 114.9, 114.6, 112.5, 112.2 (7d, C-3, C-4, C-'2, C-'4, C-'5, C- 6, C-'6), 127.2 (s, C-2), 55.5, 55.1 (2q, 2 x O<u>C</u>H$_3$), 52.0 (q, CO$_2$<u>C</u>H$_3$), 47.4 (d, α-<u>C</u>H), 47.1 (t, <u>C</u>H$_2$Ar).

Mass data

<u>m/z</u> (%): 328 (M^+, 10), 298 (52), 220 (65), 267 (30), 177 (100).

Accurate Mass measurement

Found: 328.1309 $C_{19}H_{20}O_5$ requires:

328.1311

(b) 9-Ethoxycarbonyl-9,10-dihydro-2,7-dimethoxyphenanthrene (86) as a viscous oil (0.1g, 6.3%).

I.R.

$\gamma_{max}(cm^{-1})$: 1733, 1600

^1H n.m.r.

δ(ppm, $CDCl_3$): 7.15 - 6.95 (m, 2H, 4-H, 5-H), 6.75 - 6.59 (m, 4H, 1-H, 3-H, 6-H, 7-H), 3.75 (q, 2H, OCH_2CH_3, J = 7Hz), 3.71, 3.65 (2s, 6Hz, 2 x OCH_3), 3.60 - 3.05 (m, 3H, $ArCH_2CH$), 1.24 (q, 3H, OCH_2CH_3, J = 7Hz).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 174.4 ($CO_2C_2H_5$), 158.4, 158.3 (2s, C-2, C-7), 137.7, 136.4, 132.6, 131.5 (4s, C-4a, C-4b, C-8a, C-10a), 130.7, 129.1 (2d, C-4, C-5), 115.6, 115.3, 112.3, 111.7 (4d, C-1, C-3, C-6, C-8), 55.2 (q, 2 x OCH_3), 52.1 (q, OCH_2CH_3), 48.8 (d, $ArCH_2CH$), 39.0 (t, OCH_2CH_3), 35.1 (t, $ArCH_2CH$).

Mass data

m/z (%): 312 (M^+, 22), 272 (14), 252 (100), 253 (34), 223 (32).

Accurate mass measurement

Found: 312.1362 $C_{19}H_{20}O_4$ requires:

312.1362

E-1-(3,4-Dimethoxyphenyl)-2-(3,4-dimethoxy-5-methylphenyl)ethane (108)

4-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (50, 3.0g, 0.0083 mol) was intimately mixed with N,N'-dimethylurea (0.7g, 0.0079 mol) and heated at 200° for 3 hours. The residue was then dissolved in chloroform (10 cm^3) and filtered through a column of silica (50 g). Evaporation of the solvent afforded an oil which slowly crystallised and was recrystallised from methanol to give the title compound as colourless prisms (1.8g, 68%).

m.p. 115 - 116°

U.V.

λ_{max}(nm): 300, 337

I.R.

γ_{max}(cm^{-1}): 1610, 1605

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 6.6 - 7.25 (m, 7H, aromatics, CH=CH), 3.84, 3.81 (2s, 12H, 4 x OCH_3), 2.38 (s, 3H, C-CH_3).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 149.1, 148.6, 148.4, 147.4, (4s, C-3, C-4, C-'3, C-'4), 131.1, 128.8, 128.6 (3s, C-1, C-'1, C-2), 128.4, 127.8, 124.6, 119.4, 113.6, 111.5, 109.2 (7d, C-6, C-3, C-'2, C-'5, C-'6, CH=CH), 55.9 (b.q, 4 x OCH_3), 19.3 (q, C-CH_3).

Mass data

m/z (%): (E1) 314 (M^+, 100), 299 (24).

Found: C, 72.7; H, 6.7 $C_{19}H_{22}O_4$ requires:
C, 72.6; H, 7.05%

2-(2-Hydroxymethyl-5-methoxyphenyl)-3-(3-methoxyphenyl)-N-methylpropionamide (123)

6-Methoxy-4-(3-methoxybenzyl)isochroman-3-one (84, 1.2g, 0.004 mol) in 33% methylamine in ethanol (80 cm^3) was heated at reflux for five hours. Removal of the reagent and solvent gave a yellow oil which chromatographed on silica using 5% methanol in dichloromethane as eluant to yield the title compound as a colourless oil (0.94g, 71%).

U.V.

λ_{max}(nm): 221, 274

I.R.

γ_{max}(cm^{-1}): 3250 (OH), 1667 (C=O), 1610

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 7.1 - 7.0 (m, 4H, aromatics), 6.61 (br. m, 1H, NH), 6.70 - 6.52 (m, 3H, aromatics), 4.42 (2d, 2H, $C\underline{H}_2OH$, J_{gem}=10Hz), 4.15 - 3.40, 2.95 (AMX system, 3H, $C\underline{H}C\underline{H}_2$), 3.70, 3.61 (2s, 6H, 2 x $OC\underline{H}_3$), 3.3 (br.s, 1H, OH), 2.56 (d, 3H, NH $C\underline{H}_3$, J = 4Hz).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 173.9 (s, C=O), 159.8, 159.3 (2s, C-'3, C-5), 142.2, 141.4, 140.0 (3s, C-1, C-'1, C-2), 131.0, 130.5, 129.1, 121.2, 114.5, 113.0, 111.5 (7d, C-3, C-4, C-6, C-'2, C-'4, C-'5, C-'6), 75.8 (t, $\underline{C}H_2$-OH), 55.2, 54.9, (2q, 2 x $OC\underline{H}_3$), 48.8 (d, $\underline{C}HCO$), 38.7 (t, $\underline{C}H_2$-Ar), 26.1 (q, $NC\underline{H}_3$).

Mass data

m/z (%): 329 (M^+, 4), 253 (100), 121 (56).

Accurate mass measurement

Found: 329.1627 $C_{19}H_{23}NO_4$ requires:

329.1627

2-(2-Hydroxymethyl-5-methoxyphenyl)-3-(3-methoxyphenyl)-N-methylpropylamine (124)

2-(2-Hydroxymethyl-5-methoxyphenyl)-3-(3-methoxyphenyl)-N-methylpropionamide (123, 1.8g, 0.0055 mol) in dry tetrahydrofuran (30 cm^3) was added dropwise to a well stirred slurry of lithium aluminium hydride (0.27g,0.0073mol) in dry tetrahydrofuran (90 cm^3). The mixture was then heated at reflux for 11 hours, then cooled and treated with 30% sodium potassium tartarate in water (60 cm^3). The organic layer was decanted off and the aqueous phase extracted with ethyl acetate (3 x 30 cm^3). The combined organic layer and extracts were then washed with water (2 x 20 cm^3), dried over magnesium sulphate, and evaporated to give a yellow oil. This material was chromatographed on basic alumina using 3% methanol in dichloromethane as eluant to yield the title amine as a colourless oil (1.6g, 93%).

U.V.

λ_{max}(nm): 215, 250

I.R.

γ_{max}(cm^{-1}): 3670, 3500, 1600

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 7.25 - 6.60 (m, 7H, aromatics), 4.65, 4.22, (2d, 2H, $C\underline{H}_2OH$, J_{gem}=11.5Hz), 4.20 (br.s, 2H, O$\underline{H}$, N$\underline{H}$, eliminated by D_2O), 3.81, 3.75, (2s, 6H, 2 x $OC\underline{H}_3$), 2.95 - 2.59 (m, 5H, $Ar\underline{CH}_2$-$\underline{CH}$-$\underline{CH}_2$), 2.18 (s, 3H, $NC\underline{H}_3$).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 159.8, 159.5 (2s, C-5, C-'3), 143.6, 141.3 (2s, C-1, C-'1), 133.0 (s, C-2), 131.4, 129.3, 121.2, 114.6, 112.2, 111.4, 111.1 (7d, C-3, C-4, C-'2, C-'4, C-'5, C-6, C-'6), 62.4, (t, $\underline{C}H_2OH$), 56.8 (t, $\underline{C}H_2N$), 55.2, 55.0 (2q, 2 x $OC\underline{H}_3$), 42.7 (d, $\underline{C}H$-CH_2), 40.4 (t, CH-$\underline{C}H_2$), 36.1 (q, $NC\underline{H}_3$).

Mass data

m/z (%): 315 (M^+, 5), 254 (12), 178 (8), 121 (40).

Accurate mass measurement:

Found: 315.3979 $C_{19}H_{25}NO_3$ requires:
315.3970

2-Methyl-4-(3-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (125).

2-(2-Hydroxymethyl-5-methoxyphenyl)-3-(3-methoxyphenyl)-N-methylpropanamine (124, 1.0g, 0.0031 mol) and p-toluenesulphonic acid (0.6g, 0.0032 mol) in dry benzene (100 cm^3) were heated together in a Dean-Stark apparatus for 9 hours. The mixture was then cooled and agitated with aqueous 2M sodium bicarbonate solution (50 cm^3). The organic phase was then separated, and the aqueous layer extracted with benzene (2 x 25 cm^3). The combined organic layer

and extracts were then dried over magnesium sulphate, and evaporated to afford a gum which gave the title compound as a colourless oil, after chromatography on basic silica, using 5% methanol in dichloromethane as eluant (0.85, 90%).

I.R.

$\gamma_{max}(cm^{-1})$: 1600, 1595

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 7.20 - 6.95 (m, 3H, aromatics). 6.81 - 6.59 (m, 4H, aromatics), 4.00 (dd, 2H, 1-H, J_{gem}=8Hz), 3.70 (s, 6H, 2 x OCH_3), 3.22 - 2.72 (m, 5H, CH_2Ar, 3-H, 4-H), 2.42 (s, 3H, NCH_3).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 158.2 (s, C-'3, C-6), 141.4, 139.0 (2s, C-'1, C-8a), 132.1 (s, C-4a), 130.2, 129.0, 115.9, 115.5, 115.2, 111.1, 110.9 (7d, C-5, C-7, C-'2, C-'4, C-'5, C-8, C-'6), 58.1 (t, C-1), 55.2 (q, 2 x OCH_3), 46.1 (d, C-4), 41.3 (t, C-3), 39.3 (q, NCH_3), 36.5 (t, CH_2Ar).

Mass data

m/z (%): 297 (M^+, 60), 254 (17), 101 (100)

Accurate mass measurement

Found: 297.1741 $C_{19}H_{23}NO_2$ requires:

297.1729

Electrochemical oxidation of 2-methyl-4-(3-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (125)

(i) In acetonitrile-methanol

The isoquinoline (125, 1.0g,0.0034 mol) was dissolved in 0.1M solution of sodium perchlorate in acetonitrile-methanol (3:1) and electrolysed at an anode potential of + 1.2 - 1.3 volts and a cell current of 200mA for 2.30 hours. After this time, the anolyte was separated and diluted with water (100cm^3) and evaporated to low bulk. The dark residue was dissolved in dichloromethane (20 cm^3), washed with water (2 x 5 cm^3) and finally dried over magnesium sulphate. Removal of the solvent by evaporation left a brown gum which was chromatographed by basic silica using 5% methanol in dichloromethane as eluant to give 10,11-dihydro-2,8-dimethoxy-5,10-(N-methylazaethano)-5H-dibenzo[a,d]cycloheptene (127) as a pale yellow oil (0.65g, 67%).

I.R.

$\gamma_{max}(cm^{-1})$: 1600, 1590

^1H n.m.r.

δ(ppm, $CDCl_3$): 7.05 - 6.49 (2ABC system, 6H, aromatics), 4.25 (s, 1H, 10-H), 3.75, 3.68 (2s, 6H, 2 x OCH_3), 3.4 - 2.8 (m, 5H, 5-H, 11-H, CH_2NMe), 2.4 (s, 3H, NCH_3).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 159.2, 159.0 (2s, C-2, C-8), 139.1, 137.0, 135.5 (3s, C-4a, C-5a, C-9a), 130.6 (s, C-11a), 130.2, 125.4, 116.6, 112.5, 111.1, 111.0 (6d, C-1, C-3, C-4, C-6, C-7, C-9), 68.3 (d, C-10), 55.5 (t, CH_2NCH_3),55.0 (q, 2 x OCH_3), 43.6 (q, NCH_3), 41.2 (t, C-11), 37.4 (d, C-5).

Mass data

m/z (%): 295 (M^+, 22), 252 (100), 209(15), 174.1 (31)

Accurate mass measurement

Found: 295.1570 $C_{19}H_{21}NO_2$ requires:

295.1572

(ii) In acetonitrile-hydrofluoroboric acid

The isoquinoline (125. 1.0g, 0.0034 mol) was electrolysed in acetonitrile (400 cm^3) and hydrofluorboric acid (2 cm^3) containing tetrabutylammonium fluoroborate (2.0g) at a potential difference 1.5 volts (vs SCE) until two Faradays of electricity per mole of substrate had been consumed. Water (10 cm^3) was then added and the mixture evaporated to near dryness, sodium carbonate was added in small portions to the aqueous residue until no more carbon dioxide was evolved. The mixture was extracted with chloroform (2 x 25 cm^3), dried over magnesium sulphate, and the solvent evaporated to afford a gum. This was purified by chromatography on basic silica using 5% methanol in dichloromethane as eluant to give an oil which proved to be a diastereomeric mixture of dehydrodimers (129) of the starting material.

I.R.

γ_{max}(cm^{-1}): 1600

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 7.20 - 6.59 (m, 6H, aromatics), 4.00 (dd, 2H, 1-H), 3.75, 3.70 (2s, 6H, 2 x OCH_3), 3.40 - 2.56(m, 5H, 3-H, 4-H, CH_2Ar), 2.45 (m, 3H, NCH_3).

Mass data

m/z (%): (E1) 296 (M^+, 20), 295 (80), 294 (50)

(C1) 593 (M + 1)

2,2-Dimethoxy-N-(3,4-dimethoxybenzylidene)ethylamine (112)

Aminoacetaldehydedimethylacetal (10.5g, 0.1 mol) and 3,4-dimethoxybenzaldehyde (36, 16.6g, 0.1 mol) in dry benzene (100 cm^3) were heated under reflux for 5 hours with constant removal of water using a Dean-Stark apparatus. The solvent was then removed by evaporation under reduced pressure to yield a colourless oil which was triturated with cold absolute ethanol (25 cm^3). This gave a crystalline product which was recrystallised from absolute ethanol as colourless needles of the title compound (21.2g, 83%).

m.p. 56 - 57° lit.[74], m.p. 57 - 58°

I.R.

γ_{max} (cm^{-1}): 1840 (C=N)

^1H n.m.r.

δ(ppm, $CDCl_3$): 8.21 (br.s, 1H, ArC<u>H</u>N), 7.46 (d, 1H, 2-H, <u>J</u> = 2Hz), 7.19 (dd, 1H, 6-H, J_{gem} = 16Hz), 6.88 (d, 1H, 5-H, <u>J</u> = 16Hz), 4.69 (t, 1H, C<u>H</u>-$(OCH_3)_2$, <u>J</u> = 6Hz), 3.92 (2s, 6H, 2 x O<u>C</u>H_3), 3.78 (d, 2H, N-<u>C</u>H_2, <u>J</u> = 6Hz), 3.44 (s, 6H, 2 x O<u>C</u>H_3-CH).

Mass data

m/z (%): 253 (M^+, 50), 222 (50), 190 (36), 151 (100).

2,2-Dimethoxy-N-(3,4-dimethoxybenzyl)ethylamine (113)

2-2-Dimethoxy-N-(3,4-dimethoxybenzylidene)ethylamine (112, 25.3g, 0.1 mol) in 95% ethanol (150 cm^3) was treated with sodium borohydride (8.0g, 0.2 mol) in portions, then, the mixture was stirred overnight at room temperature. Water (300 cm^3) was added and the mixture extracted with dichloromethane (2 x 100 cm^3). The combined organic extracts were washed with water (2 x 100 cm^3) and dried over magnesium sulphate. Evaporation of the solvent left a yellow oil which was distilled as colourless oil (17.3g, 67%). B.p. 150 - 160°/0.6 mm Hg lit.[74], b.p. 150 - 160/0.6 mm Hg

I.R.

$\gamma_{max}(cm^{-1})$: 3530 - 3320 (NH), 2940, 2840, 1610

^1H n.m.r.

δ(ppm, $CDCl_3$): 7.30 (s, 1H, 2-H), 7.0 - 6.7 (m, 3H, aromatics, NH (removed by D_2O)), 4.70 (t, 1H, $\underline{CH}$-$(OCH_3)_2$ $\underline{J}$ = 7Hz), 4.0 - 3.8 (3s, 8H, 2 x OCH_3 + CH_2Ar), 3.40 (s, 6H, 2 x OCH_3), 2.80 (d, 2H, CH_2CH, $\underline{J}$ = 7Hz).

Mass data

m/z (%): 255 (M^+, 30), 223 (35), 180 (20), 151 (100).

1,4-Dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzylidene)isoquinolinium chloride (115).

3,4-Dimethoxybenzaldehyde (36, 18.3g, 0.11 mol), freshly recrystallised from absolute ethanol, and 2,2-dimethoxy-N-(3,4-dimethoxybenzyl)ethylamine (113, 25.5g, 0.1 mol) were dissolved in a mixture of ethanol (40 cm^3) and 6N hydrochloric acid (40 cm^3).

This solution was heated and the mixture set aside for 2 - 4 days. A red solid product which formed was collected and recrystallised from ethanol (50 cm^3) to yield red needles of the title compound (28.7g, 76%).

m.p. 184° lit.[74], m.p. 185° (dec.)

I.R.

$\gamma_{max}(cm^{-1})$: 3350 (br, NH), 1650 (C=N), 1605 , 1590, 1370

^1H n.m.r.

δ(ppm, $CDCl_3$): 8.65 (s, 1H, NHCH), 8.3 (s, 1H, NH, (removed by D_2O)), 7.35 - 6.55 (m, 6H, aromatics, =CH), 4.90 (br.s, 2H, CH_2Ar), 4.05 - 3.75 (m, 12H, 4 x OCH_3).

6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline (116)

1,4-Dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzylidene)isoquinolinium chloride (115, 20.0g, 6.53 mol) was dissolved in ethanol (200 cm^3) and anhydrous potassium carbonate (20.0g) was added. The mixture was heated under reflux conditions for 5 hours, and was then filtered. The solvent was removed by evaporation and the residue was dissolved in dichloromethane (100 cm^3). The solution was then washed with water (2 x 50 cm^3), dried over magnesium sulphate. Evaporation of the solvent left a brown oil which was chromatographed over silica using dichloromethane as eluant to yield the product as a white solid (13.3g, 74%).

m.p. 126 - 127° lit.[74], m.p. 127 - 128°

U.V.

λ_{max}(nm): 238, 282, 288, 313, 326

I.R.

γ_{max}(cm^{-1}): 2830, 1595, 1250, 1025

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 9.03 (br.s, 1H, 1-H), 8.33 (s, 1H, 3-H) 7.20, 7.10 (2s, 2H, 5-H, 8-H), 6.8 - 6.6 (m, 3H, '2-H, '5-H, '6-H), 4.20 (s, 2H, CH_2Ar), 3.95, 3.84, 3.79, 3.72 (4s, 12H, 4 x OCH_3).

Mass data

m/z (%): 393 (M^+, 100), 324 (19), 308 (11).

2-Methyl-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinolinium iodide (117).

7,6-Dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline (116, 1.0g, 0.003 mol) and methyliodide (0.4g, 0.003 mol) in hot acetone (100 cm^3) were heated under refluxed conditions for 30 minutes. After cooling the reaction mixture, the salt was removed by filtration and recrystallised from ethanol to give yellow needles (0.9g, 58%).

m.p. 204° lit.[74], m.p. 204 - 208°

U.V.

λ_{max}(nm): 210, 259, 290, 322.

I.R.

γ_{max}(cm^{-1}): 1635

^{1}H n.m.r.

δ(ppm, DMSO): 9.48 (s, 1H, 1-H), 8.49 (s, 1H, 3-H), 7.77 (s, 1H, 5-H), 7.61 (s, 1H, 8-H), 7.1 - 6.8 (complex, 3H, aromatics), 4.45 (s, 2H, $C\underline{H}_2Ar$), 4.39 (s, 3H, $NC\underline{H}_3$), 4.01, 3.96, 3.72, 3.68 (4s, 12H, 4 x $OC\underline{H}_3$).

Mass data

m/z (%): 339 (M^+, $M-CH_3I$), 151 ($ArCH_2$), 142 (CH_3I), 127 (I).

2-Methyl-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (16)

2-Methyl-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinolinium iodide (117, 4.8g, 0.01 mol) in ethanol (200 cm^3) was treated with sodium borohydride (8.0g) in portion over 30 minutes. After stirring at room temperature overnight, 2N hydrochloric acid (200 cm^3) was added cautiously and when the mixture had become homogenous, 2M sodium hydroxide solution was added until the solution was alkaline to litmus paper. The cooled solution was extracted with dichloromethane (4 x 50 cm^3) and the combined organic extracts were washed with water (2 x 50 cm^3) and finally dried over magnesium sulphate. Evaporation of the solvent left an oil which was crystallised from ethanol as a white solid (2.57g, 72%).
m.p. 96° lit.[74], m.p. 96°

U.V.

λ_{max}(nm): 213, 233, 286, 289

I.R.

γ_{max}(cm^{-1}): 1130 (aromatic ether)

^{1}H n.m.r.

δ(ppm, DMSO): 6.9 - 6.6 (complex, 5H, aromatics), 3.76, 3.74, 3.72, 3.68 (4s, 12H, 4 x $OC\underline{H}_3$), 2.28 (s, 3H, $NC\underline{H}_3$), 3.6 - 2.1 (complex, 7H, aliphatics)

Mass data

m/z (%): 357 (M^+, 43), 342 (12), 219 (40), 205 (100).

Electrooxidation of 2-methyl-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (16)

The 2-methyl-tetrahydroisoquinoline (16, 0.5g, 0.0014 mol) in acetonitrile (150 cm^3) containing hydrofluoroboric acid (1 cm^3) and tetraethylammoniumtetrafluoroborate (1.0g) was electrolysed in a simple one compartment cell at a constant current of 200mA, until 4 Faradays of electricity per mole of substrate had been consumed (45 minutes). Water was added and the solvent evaporated under reduced pressure. Methanol (2 cm^3) was then added and the crystals of electrolyte which had formed were filtered off. The mother liquorwas diluted with chloroform (20 cm^3) and washed with 2M aqueous ammonia (2 x 10 cm^3). The organic phase was dried over magnesium sulphate. The solvent was evaporated to give an oil which was chromatographed on silica using (3:1) ethylacetate in methanol as eluant to give

(a) the phenolic isoaporphine (131, 0.15g, 31%).

m.p. 208 - 210^o (ethanol)

U.V.

λ_{max}(nm): 280, 302

I.R.

$\gamma_{max}(cm^{-1})$, 3400 - 3150 (br), 1595

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 7.90 (s, 1H, 11-H), 6.71 (s, 1H, 8-H), 6.54 (s, 1H, 3-H), 3.86 (s, 3H, 10-OCH_3), 3.85 (s, 3H, 9-OCH_3), 3.54 (s, 3H, 5-OCH_3), 3.78 (d, 1H, 4β-H, J = 15Hz), 3.39 (dd, 1H, 7β-H , J_1 = 12Hz, J_2 = 5Hz), 3.25 (d, 1H, 3α-H, J = 15Hz), 3.06 (dd, 1H, 6β-H, J_1 = 10Hz, J_2 = 5Hz), 2.86 (m, 1H, 6a-H), 2.50 (dd, 1H, 7α-H, J_1 = 12Hz, J_2 = 5Hz), 2.43 (s, 3H, NCH_3), 2.08 (dd, 1H, 6α-H, J_1 = 10Hz, J_2 = 5Hz).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 148.1, 147.8, 147.5 (3s, C-1, C-9, C-10), 142.4 (s, C-2), 130.8, 130.0, 126.4, 125.9, 124.3 (5s, C-3a, C-3b, C-7a, C-11a, C-11b), 110.9, 110.8, 109.5 (3d, C-3, C-8, C-11), 60.2 (q, 1-OCH_3), 58.6 (t, C-4), 57.8 (t, C-6), 56.0, 55.8, (2q, 9-OCH_3, 10-OCH_3), 45.9 (q, NCH_3), 34.4 (d, C-6a), 33.7 (t, C-7).

Mass data

m/z (%): 341 (M^+, 80), 298 (30)

Found: C, 70.2; H, 6.8; N, 3.9 $C_{20}H_{23}NO_4$ requires:
C, 70.4; H, 6.8; N, 4.1%

Nuclear Overhauser experiments

signal irradiated	observed enhancements
10-OCH_3 (3.86 ppm)	11-H (7.90 ppm) 5%
11-H (7.90 ppm)	1-OCH_3 (3.54 ppm) 10%
1-OCH_3 (3.54 ppm)	1-H (7.90 ppm) 8%
3-H (6.54 ppm)	4β-H (3.70 ppm) 12%
4β-H (3.78 ppm)	3-H (6.54 ppm) 2%

(b) The Tetramethoxyisoaporphine (130) as a colourless solid (0.03g, 6%).

m.p. 113 - 114° lit.[61], m.p. 113 - 114°

U.V.

λ_{max}(nm): 235, 281, 305

I.R.

γ_{max}(cm^{-1}): 1590

^{1}H n.m.r.

δ(ppm, $CDCl_3$):8.14 (s, 1H, 11-H), 6.73 (s, 1H, 8-H), 6.53 (s, 1H, 3-H), 3.91 (s, 3H, 9-OCH_3), 3.90 (s, 3H, 10-OCH_3), 3.87 (s, 3H, 2-OCH_3), 3.66 (s, 3H, 1-OCH_3), 3.2 - 2.0 (m, 7H, aliphatic protons), 2.46,(s, 3H, NCH_3).

Mass data

m/z (%): 355 (M^+, 16), 312 (14), 297 (44), 281 (69), 243 (100)

Found: C, 69.8; H, 6.7; N, 3.7 calculated for $C_{21}H_{25}NO_4$

C, 71.0; H, 7.1; N, 3.9%

2-Benzyl-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinolinium bromide (118)

6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline (116, 7.3g, 0.022 mol) was dissolved in hot Analar acetone (60 cm^3) and benzyl bromide (4.2g, 0.024 mol) was added. The mixture was heated under reflux conditions for 3 hours, after this time, the salt was removed by filtration and recrystallised from ethanol to give the title compound as colourless prisms (9.8g, 87%).

m.p. 127 - 128° lit.[15], m.p. 127 - 130°

U.V.

λ_{max}(nm): 258, 285, 319

I.R.

$\gamma_{max}(cm^{-1})$: 2840, 1260, 1025

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 9.97 (s, 1H, 1-H), 8.90 (s, 1H, 3-H), 7.97 (s, 1H, 8-H), 7.77 (s, 1H, 5-H), 7.8 - 7.5 (m, 5H, $NCH_2C_6\underline{H}_5$), 7.1 (br.s, 1H, '2-H), 6.98 (s, 2H, '6-H, '5-H), 6.02 (s, 2H, $NCH_2C_6H_5$), 4.55 (br.s, 2H, CH_2Ar), 4.13, 4.04, 3.77, 3.74 (4s, 12H, 4 x OCH_3).

Mass data

m/z (%): 339 (M^+, 29), 91 (100).

2-Benzyl-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (119)

2-Benzyl-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinolinium bromide (118, 3.2g, 0.0063 mol) in ethanol (100 cm^3) was treated with sodium borohydride (1.0g, 0.026 mol) in portion over 30 minutes. After stirring at room temperature overnight, 2M hydrochloric acid (100 cm^3) was added cautiously, and when the mixture had become homogenous, 2M sodium hydroxide solution was added until the solution was alkaline to litmus paper. The cooled solution was extracted with dichloromethane (4 x 50 cm^3) and the combined organic extracts were washed with water (2 x 50 cm^3) and finally dried over magnesium sulphate. Evaporation of the solvent left an oil which was crystallised from ethanol as a white solid (2.2g, 81%).

m.p. 106 - 107° lit.[15], m.p. 106 - 107°

U.V.

λ_{max}(nm): 239, 283

I.R.

γ_{max} (cm^{-1}): 1605, 1590, 1510, 1135

^1H n.m.r.

δ(ppm, $CDCl_3$): 7.5 - 7.2 (m, 5H, $NCH_2C_6\underline{H}_5$)6.8 - 6.5 (m, 5H, 5-H, 8-H, '2-H, '5-H, '6-H), 3.9 - 3.5 (2s, 12H, 4 x $OC\underline{H}_3$), 3.6 (br.s, 2H, 1-H), 3.7 - 3.3 (AB, 2H, $C_6H_5C\underline{H}_2N$, J= 18Hz), 3.0 - 2.3 (m, 5H, 3-H, 4-H, $C\underline{H}_2Ar$).

Mass data

m/z (%): 433 (M^+, 12), 432 (21), 342 (100), 314 (10), 299 (16), 281 (62), 151 (21).

The hydrochloride salt was prepared by adding a solution of hydrogen chloride in diethyl ether to a solution of the base (3.7g, 0.0085 mol) in toluene (30 cm^3). The product was recrystallised from methanol to yield the salt as fine colourless needles (120, 3.2g, 82%).

m.p. 217 - 218° lit.[15], m.p. 218 - 219°

I.R.

$\gamma_{max}(cm^{-1})$: 2500 - 2200 (br. $\overset{+}{N}H$), 2830, 1260, 1025

1,2,3,4-Tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline hydrochloride (121)

2-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl) isoquinolinium chloride (120, 0.4g, 0.001 mol) was dissolved in absolute ethanol (200 cm^3) and hydrogenated at atmospheric pressure over 10% palladium on charcoal (0.1g) as catalyst for 24 hours. The mixture was filtered through Kieselguhr and the solvent removed by evaporation to leave solid which was crystallised from ethanol as colourless needles (0.31g, 76%).

m.p. 137° lit.[15], m.p. 136 - 140°

U.V.

λ_{max}(nm): 234, 282

I.R.

$\gamma_{max}(cm^{-1})$: 2800 - 2300, 1590

^1H n.m.r.

δ(ppm, $CDCl_3$): 6.9 - 6.6 (m, 3H, '2-H, '5-H, '6-H), 6.50 (s, 2H, 5-H, 8-H), 3.9 - 3.7 (m, 14H, 4 x OCH_3, 1-H), 3.0 - 2.8 (m, 5H, 3-H, 4-H, CH_2Ar).

Mass data

m/z(%): 343 (M^+, 32), 192 (100), 161 (16), 151 (16).

Acetic formic anhydride

Sodium formate (3g, 0.041 mol) was dissolved in anhydrous ether (250 cm^3). Acetyl chloride (2.9g, 2.6 ml, 0.0037 mol) was added within five minutes at room temperature. The mixture was stirred overnight, then evaporation of the solvent left an oil product which was distilled at 28°/10-20 mmHg to give the title compound as colourless oil.
lit.[75], b.p. 28°/10-20 mmHg

2-Formyl-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (136, R = H)

(a) 4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (121, 0.5g, 0.0015 mol) was treated with a mixture of chloroform (25 cm^3), water (3 cm^3) and sodium carbonate (0.3g). After stirring for one hour, the chloroform layer was dried over magnesium sulphate. Evaporation of the solvent left an oily compound which was shown to be the free base of isoquinoline.

(b) This compound (122, 0.5g, 0.0015 mol) and formic acetic anhydride (7.0 cm^3) were dissolved in dry benzene (25 cm^3) and the mixture was heated under reflux condition for 3 hours under nitrogen, then water (10cm^3), 2M sodium bicarbonate (20 cm^3) were added. The organic phase was separated, washed with water (2 x 20 cm^3), and finally dried over magnesium sulphate. Evaporation of the solvent left a yellow oil which was purified by chromatography using ethyl acetate as eluant to give a white compound (0.38 g, 70%).

m.p. 115 - 117° lit.[12], m.p. 115 - 117°

I.R.

$\gamma_{max}(cm^{-1})$: 1600, 1610, 1585

^1H n.m.r.

δ(ppm, $CDCl_3$): 8.36, 8.07 (2s, 1H, C<u>H</u>O), 6.9 - 6.5 (m, 4H, 5-H, '2-H, '5-H, '6-H), 6.44 (s, 1H, 8-H), 5.1, 4.21 (AB system, 2H, 1-H, <u>J</u> = 12Hz), 4.0 - 3.54 (m, 1H, 4-H), 3.86, 3.78 (2s, 12H, 4 x O<u>CH</u>$_3$), 3.78 (m, 2H, 3-H), 3.2 - 2.46 (m, 2H, <u>CH</u>$_2$Ar).

Mass data

<u>m/z</u> (%): 371 (M^+, 21), 220 (74), 151 (100).

Electrochemical oxidation of 2-formyl-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (136, R = H).

Th N-formylisoquinoline (136, R = H, 1.1g, 0.0029 mol) in 0.1M sodium perchlorate in acetonitrile solution (300 cm^3) was oxidised at an anode potential of + 1.0 - 1.1 volts <u>vs</u> (SCE) until two Faradays of electricity per mole of substrate had been consumed.

Water (10 cm^3) was added to the anolyte which was then evaporated to near dryness. The residue was mixed with chloroform (55 cm^3). The organic phase separated, washed with water (2 x 20 cm^3), dried over magnesium sulphate and evaporated to afford a brown gum. This material was chromatographed on silica using chloroform as eluant to give a colourless crystalline solid (0.44g, 50%) of 2,3,6,7-tetramethoxyphenanthrene (137).

m.p. 178° lit.[76], m.p. 178°

U.V.

λ_{max}(nm): 251, 282, 306

I.R.

γ_{max}(cm^{-1}): 1660

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 7.76, 7.52, 7.20 (3s, 6H, aromatics)
408, 3.98 (2s, 14H, 4 x OCH_3, HC = CH).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 149.5, 149.0 (2s, C-2, C-3, C-6, C-7), 129.0, 127.1 (2s, C-4a, C-4b, C-8a, C-10a), 124.3, 108.6 (2d, C-1, C-4, C-5, C-8), 103.3 (d, C-9, C-10), 56.2, 55.9 (2q, 4 x OCH_3).

Mass data

m/z (%): 298 (M^+, 40), 169 (49), 166 (100).

Accurate mass measurement

Found: 298.1202 calculated for $C_{18}H_{18}O_4$:
298.1205

Found: C, 72.3; H, 6.0 calculated for $C_{18}H_{18}O_4$
C, 72.5; H, 6.1%

2-Ethoxycarbonyl-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (138).

4-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (121, 0.5g, 0.0015 mol) was treated with a mixture of chloroform (25 cm^3), water (3 cm^3), and sodium carbonate (0.3g). After stirring for one hour, ethyl chloroformate (0.16g, 0.0015 mol) was added and the mixture left stirring for another 3 hours. Then the organic phase was separated, washed with water (2 x 25 cm^3), dried over magnesium sulphate. Evaporation of the solvent gave a gum which was chromatographed by passage through a silica column using ethyl acetate as eluant. This gave a colourless solid (0.5 g, 83%).

m.p. 153 - 154°

U.V.

λ_{max}(nm): 240, 290

I.R.

γ_{max}(cm^{-1}): 1690, 1610

^1H n.m.r.

δ(ppm, $CDCl_3$): 6.70 (m, 3H, aromatics), 6.51, 6.30 (2s, 2H,

aromatics), 4.75, 4.26 (dd, 2H, 1-H, J_{gem} = 10Hz), 4.20 (q, 2H, OCH_2CH_3, J = 7Hz), 3.87, 3.85 (2s, 12H, 4 x OCH_3), 3.80, 3.4 - 2.7 (m, 5H, 3-H, 4-H, CH_2Ar), 1.31 (t, 3H, CH_3CH_2O, J = 7Hz).

^{13}C n.m.r.

δ($CDCl_3$, ppm): 156.2 (s, C=O), 148.9, 148.1, 147.7 147.5 (4s, C-6, C-7, C-'3, C-'4), 132.7, 130.8, 124.7 (3s, C-'1, C-4a, C-8a), 121.7, 113.2, 112.1, 111.4, 109.0 (5d, C-8, C-'2, C-'5, C-'6, C-6), 61.4 (t, OCH_2CH_3), 55.9 (q, 4 x OCH_3), 45.6 (t, C-1), 44.8 (t, C-3), 41.0 (d, t, C-4, CH_2Ar), 14.8 (q, CH_3CH_2).

Mass data

m/z (%): 415 (M^+, 8), 264 (100), 151 (23)

Accurate mass measurement

Found: 415.2000 $C_{23}H_{29}NO_6$ requires:
415.1995

Found: C, 66.4; H, 7.0; N, 3.5 $C_{23}H_{29}NO_6$
requires: C, 66.5; H, 7.0; N, 3.4%

Electrochemical oxidation of 2-ethoxycarbonyl-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (138).

(i) The isoquinoline (138, 1.2g, 0.0029 mol) in 0.1M sodium perchlorate in acetonitrile solution (250 cm^3) was electrolysed at an anode potential of + 0.95 volt vs (SCE) and cell current of 100mA until two Faradays of electricity per mole of substrate had been consumed. The anolyte was then diluted with water (10 cm^3) and the mixture evaporated under reduced pressure to near dryness.

The residue was extracted with dichloromethane (3 x 25 cm^3) and the combined extracts were washed with water (2 x 10 cm^3), dried over magnesium sulphate and evaporated to give dark brown gum which was purified by chromatography over silica usimg chloroform as eluant to give tetramethoxyphenanthrene (137)[75] as a white solid (0.30g, 35%).

(ii) A similar experiment was carried out using 0.1M of sodium perchlorate in acetonitrile-methanol (5:1) as the electrolyte system. This gave the same tetramethoxyphenanthrene (137, 0.33g, 28%).

2-Methylsulphonyl-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (139)

1,2,3,4-Tetrahydro-7,6-dimethoxy-4-(3,4-dimethoxybenzyl) isoquinoline hydrochloride (121, 0.5g, 0.0015 mol) was treated with a mixture of chloroform (25 cm^3), water (3 cm^3) and sodium carbonate (0.3g). After stirring for one hour, methylsulphonyl chloride (0.15g, 0.0015 mol) was added dropwise and the mixture agitated for another 2 hours, then more chloroform (50cm^3) and water (25 cm^3) was added. The organic layer was separated then washed with water (2 x 25 cm^3) and finally dried over magnesium sulphate. Evaporation of the solvent left yellow oil which was purified by chromatography using ethyl acetate as eluant to give a white powder (0.55g, 90%).

m.p. 183 - 184°

U.V.

λ_{max}(nm): 222, 277

I.R.

$\gamma_{max}(cm^{-1})$: 1610, 1595

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 6.9 - 6.75 (complex, 3H, aromatics), 6.6,6.4 (2s,2H, aromatics), 4.7, 3.9 (2d, 2H, 1-H , J_{gem} = 16Hz), 3.9, 3.8 (2s, 12H, 4 x OCH_3), 3.75 (s, 2H, CH_2Ar), 2.95 - 2.85 (complex, 3H, 4-H, 3-H), 2.8 (s, 3H, SO_2CH_3).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 149.0, 148.1, 147.6 (3s, C-6, C-7, C-'4, C-'3), 132.4 (s, C-4a), 129.6 (s, C-8a), 123.2 (s, '1-C), 121.5 (d, C-'2), 113.5, 112.0, (2d, C-'5, C-'6), 111.6, 108.2 (2d, C-5, C-8), 56.0 (q, 4 x OCH_3), 47.6 (t, C-1), 46.2 (t, C-3), 41.3 (d, C-4), 41.0 (t, CH_2Ar), 34.1 (q, SO_2CH_3).

Mass data

m/z (%): 421 (M^+, 27), 342 (15), 270 (11), 190 (29), 151 (100).

Accurate mass measurement

Found: 421.1559 $C_{21}H_{27}NO_6S$ required

421.1560

Found: C, 59.60; H, 6.49; N, 3.23; S, 7.70; $C_{21}H_{27}NO_6S$

Required: C, 59.63; H, 6.45; N, 3.32; S, 7.60%

Electrooxidation of 2-methylsulphonyl-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (139)

The isoquinoline (139, 0.75g, 0.00178 mol) in 0.1M sodium perchlorate in acetonitrile solution (250 cm^3) was electrolysed at an anode potential of 1.1 volts vs (SCE) and a cell current of 35 mA. After the two Faradays of electricity per mole of substrate had been consumed , the anolyte was then separated, diluted with water (10 cm^3) and the mixture evaporated under reduced pressure to near dryness. The residue was extracted with chloroform (3 x 25 cm^3) and the combined extracts were washed with water (2 x 10 cm^3) and dried over magnesium sulphate. Evaporation of the solvent gave a brown dark gum, which was purified by chromatography using 20% ethyl acetate in dichloromethane to give an oil (0.3g, 40%), which appears to be mainly the dimer , possibly as a mixture of diastereomers. It was not possible to obtain this compound(s) perfectly pure. However, the following data support the structural assignment.

U.V.

λ_{max}(nm): 290, 319

I.R.

γ_{max}(cm^{-1}): 1600, 1352

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 6.65 (m, 6H, aromatics), 6.3 (br.s, 2H aromatics), 3.85 (b.s, 18H, 6 x OCH_3), 3.65 (b.s, 6H, 2 x OCH_3), 4.0 - 3.0 (m, 14H, aliphatics), 2.7 (b.s, 6H, 2 x SO_2CH_3).

Accurate mass measurement

(EI): 419.1397 $C_{21}H_{25}NO_6S$ requires:

419.1402

Mass data

(FAB): 840 (highest mass)

which appears to be mainly the dimer, possibly as a mixture of diastereomers, with perhaps some of the isoaporphine. The accurate mass spectrum (E_1) shows a species m/z 419.1397 which corresponds to the last structure ($C_{21}H_{25}NO_6S$ requires m/z 419.1402), and the ^1H n.m.r. spectrum shows a singlet at δ8.0 which corresponds to the low field shift position of the resonance of C_{11}-H in similar compounds (see p.194). Unfortunately we were unable to separate the mixture of these compounds to make definitive statements about them.

2-Cyano-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (140).

1,2,3,4-Tetrahydro-4-(3,4-dimethoxybenzyl)-6,7-dimethoxytetrahydroisoquinoline hydrochloride (121, 2.0g, 0.0058 mol) was dissolved in chloroform (25 cm^3) and washed with saturated sodium bicarbonate until no further evolution of carbon dioxide was evident. The solution was washed with water (50 cm^3) and dried over magnesium sulphate. To the solution of the free base was added dropwise a solution of cyanogen bromide (6g, 0.0058 mol) in chloroform (20 cm^3) under nitrogen. The mixture was left stirring for 3 hours then the solvent was evaporated under reduced pressure to leave a white solid. This was purified by chromatography on silica using 40% ethyl acetate in 40 - 60^o

petroleum ether as the eluting solvent system to give colourless prisms (1.8g, 84%).

m.p. 102 - 104°

U.V.

λ_{max}(nm): 230, 237

I.R.

γ_{max}(cm^{-1}): 2220, 1610, 1595

^1H n.m.r.

δ(ppm, $CDCl_3$): 6.9 - 6.69 (m, 3H, aromatics), 6.60 - 6.4 (m, 2H, aromatics), 4.20 (s, 2H, 1-H), 3.9 - 3.7 (4s, 12H, 4 x $O\underline{C}H_3$), 3.3 (m, 2H, $C\underline{H}_2Ar$), 3.0 - 2.9 (complex, 3H, 3-H, 4-H).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 149.0, 148.0, 147.7 (3s, C-'3, C-'4, C-6, C-7), 131.6, 128.4, 121.9 (3s, C-4a, C-'1, C-8a), 121.4 (s, $\underline{C}\equiv N$), 118.4, 112.7, 111.9, 111.6, 108.5 (5d, C-'2, C-'5, C-'6, C-5, C-8), 55.9 (q, 4 x $O\underline{C}H_3$), 49.4 (t, C-1), 48.8 (t, $C\underline{H}_2Ar$), 41.0 (t, C-3), 39.9 (d, C-4),

Mass data

m/z (%): 368 (M^+, 80), 217 (90), 151 (100)

Accurate mass measurement

Found: 368.1736 $C_{21}H_{24}N_2O_4$ requires:
368.1735

Found: C, 68.40; H, 6.53; N, 7.57; $C_{21}H_{24}N_2O_4$ requires:
C, 68.46; H, 6.56; N, 7.60%

Electrochemical oxidation of 2-cyano-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (140)

The base (140, 0.5g, 0.00135 mol) was dissolved in 0.1M sodium perchlorate in dry acetonitrile (300 cm^3) and electrolysed at a potential of 1.2 volts (vs SCE) until the current dropped below 10mA. Then, the anolyte was separated, water (10 cm^3) was added and the solvent evaporated to near dryness. The dark residue was dissolved in chloroform (25 cm^3), washed with water (10 cm^3) and finally dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a brown gum which was chromatographed on silica eluting with 80% ethyl acetate in 60 - 80° petroleum ether. The only component isolated was the starting material (0.3g, 60%).

2-(N-Phenylcarbamyl)-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (141).

1,2,3,4-Tetrahydro-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-isoquinoline hydrochloride (121, 0.5g, 0.0015 mol) was treated with a mixture of chloroform (25 cm^3), water (3 cm^3) and sodium carbonate (0.3g). After the mixture had been stirred for one hour, the solution was washed with water (50 cm^3) and dried over magnesium sulphate. Evaporation of the solvent left an oily compound which was shown to be the free base of the isoquinoline (122). This compound and phenyl isocyanate (0.13g, 0.0021 mol) were dissolved in dry benzene (25 cm^3) and the mixture was heated under reflux condition for 3 hours under nitrogen. Then, the solvent was evaporated under reduced pressure to give an oil which was chromatographed over silica using 20% ethyl acetate in 60 - 80° petroleum ether as eluant to give

colourless needles (0.6g, 89%).

m.p. 70 - 72°

U.V.

λ_{max}(nm): 235

I.R.

γ_{max}(cm^{-1}): 3450 (NH), 1660, 1610.

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 7.1 - 6.9 (complex, 5H, $C_6\underline{H}_5NH$), 6.85 (s, 1H, N$\underline{H}$, exchanged with D_2O), 6.8 - 6.6 (m, 3H, aromatics), 6.75 - 6.6 (m, 2H, aromatics), 4.9, 4.2 (2d,1-H, 1-H, J_{gem} = 14Hz), 3.85 - 3.7 (3s, 12H, 4 x O$\underline{CH}_3$), 3.3 - 2.7 (complex, 5H, $\underline{CH}_2$Ar, 3-H, 4-H)

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 155.5 (s, C=O), 148.9, 148.0, 147.5 (3s, C-'4, C-'3, C-6, C-7), 139.3 (s, N-$\underline{C}$ aromatics), 132.0, 129.7, 124.3 (3s, C-'1, C-4a, C-8a), 128.7, 119.8 (2d, $\underline{C}_5\underline{H}_5$), 122.8, 121.3, (2d, C-5, C-8), 112.7, 111.4, 109.1 (3d, C-'2, C-'5, C-'6). 55.9, 55.7, (2q, 4 x O$\underline{CH}_3$), 45.6, 44.6 (2t, C-1, C-3), 40.52 (d, C-4), 40.51 (t, $\underline{CH}_2$Ar).

Mass data

m/z (%): 462 (M^+, 10), 386 (6), 344 (100).

Accurate mass measurement

Found: 462.2153 $C_{27}H_{30}N_2O_5$ requires: 462.2150

Found: C, 69.99; H, 6.40; N, 5.84. $C_{27}H_{30}N_2O_5$
requires: C, 70.10; H, 6.53; N, 5.86%

Electrochemical oxidation of 2-(N-phenylcarbamyl)-4-(6,7-dimethoxy benzyl)6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (141).

The protected isoquinoline (141, 0.5g, 0.0014 mol) in 0.1M sodium perchlorate in dry acetonitrile (300 cm^3) was electrolysed at an anode potential of 1.2 volts (vsSCE) and at a current flow of 200mA until the starting material had been consumed. Then, the anolyte was separated, water (10 cm^3) was added and the mixture was evaporated to near dryness. The dark residue was dissolved in chloroform (55 cm^3), washed with water (2 x 20 cm^3) and finally dried over magnesium sulphate. Evaporation of the solvent left a brown gum, which was chromatographed over silica using 20% ethyl acetate in 60 - 80° petroleum ether as the eluant. Unfortunately no cleanly residued products were obtained and it was assumed that extensive decomposition of the starting material and/or the products had occurred. The tlc analyses of the fractions from the column all showed many spots after spraying.

2-Triphenylmethyl-4-(3,4-dimethoxybenzyl)6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinium chloride (145).

(a) 1,2,3,4-Tetrahydro-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (121, 0.5g, 0.0015 mol) was dissolved in chloroform (25 cm^3) and washed with saturated sodium bicarbonate solution until no further evolution of carbon dioxide was evident. The solution was washed with water (50 cm^3) and dried over magnesium sulphate. Evaporation of the solvent was left an

oil compound of free base (122).

(b) The free base was dissolved in dry dimethylformamide (15 cm^3) and triethylamine (3 cm^3) was added as a base. The mixture was left stirring for ten minutes, then, triphenylmethyl chloride (0.6g, 0.0023 mol) was added at 0^o under nitrogen, and the mixture was then agitated for another 4 hours. After this time the reaction mixture was washed with water (2 x 25 cm^3), the organic phase separated, dried over magnesium sulphate and evaporated to give an oil which was purified by chromatography over silica using 20% ethyl acetate in 60 - 80^o petroleum ether as eluant, to give colourless product (0.81g, 90%).

m.p. 164 - 165^o

U.V.

λ_{max}(nm): 229, 275

I.R.

$\gamma_{max}(cm^{-1})$: 1610, 1595

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 7.8 - 7.0 (complex, 15H, aromatics resonance of triphenyl groups), 6.8 - 6.39 (m, 5H, aromatics), 3.8, 3.75, 3.71, 3.70 (4s, 11H, 3 x OCH_3, 1-H), 3.60 (s, 3H, OCH_3), 3.38 - 3.2 (complex, 5H, CH_2Ar, 3-H, 4-H).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 148.8, 147.2, 146.1, 146.9, (4s, C-'3, C-'4, C-6, C-7), 142.4 (s, $C-(C_6H_5)_3$) 133.3, 130.0, 128.1 (3s, C-4a,

C-'1, C-8a), 129.4, 127.4, 126.1 (3d, aromatics carbon resonances of triphenyl group), 121.2, 121.1, 112.7, 111.5, 109.5 (5d, C-5, C-'2, C-'5, C-'6, C-8), 55.8, (q, 4 x $O\underline{C}H_3$), 52.17 (t, C-1), 52.1, (t, $C\underline{H}_2Ar$), 51.3 (t, C-3), 41.5 (d, C-4).

Mass data

m/z (%): 432 (M^+, 13), 242 (100).

Electrochemical oxidation of 2-triphenylmethyl-4-(3,4-dimethoxybenzyl) 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolinium chloride (145).

The N-triphenylmethylisoquinolinium salt (145, 0.5g, 0.0012 mol) in 0.1M sodium perchlorate in acetonitrile solution(250 cm^3) was oxidised at an anode potential of 1.65 volts (vs SCE) for 1.5 hours. Water (10 cm^3) was added to the anolyte, which was then evaporated to near dryness. The residue was extracted with dichloromethane (2 x 25 cm^3) and the combined organic extracts were dried over magnesium sulphate. Evaporation of the solvent left a yellow oily compound which was purified by chromatography over alumina eluting with 20% ethyl acetate in dichloromethane. This gave the following compounds in order of elution from the column.

(a) triphenylmethyl alcohol (144, 0.1g, 20%).

m.p. 159 - 160° lit.[77], m.p. 160 °

U.V.

λ_{max}(nm): 250

I.R.

$\gamma_{max}(cm^{-1})$: 3400 - 3300 (br.OH), 1600

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 7.21 (s, 15H, 3 x $C_6\underline{H}_5$), 2.9 (br.s, 1H, OH)

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 146.9, (s, $\underline{C}$-OH), 127.9, 127.1 (2s, 3 x $\underline{C}_6H_5$)

Mass data

m/z (%): 260 (M^+,25), 183 (100), 154 (30), 105 (90)

(b) 1,2,3,4-Tetrahydro-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy isoquinoline (122, 0.2g, 40%).[74]

U.V.

λ_{max}(nm): 238, 280, 310

I.R.

$\gamma_{max}(cm^{-1})$, 3560, 1600, 1610

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 8.3 (b.s.1H, NH), 6.7 - 6.3 (complex, 5H, aromatics), 4.10 - 3.6 (4s, 12H, 4 x $O\underline{CH}_3$), 3.8 - 3.55 (m, 7H, aliphatic resonances)

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 151.0, 148.8, 148.0, 147.7 (4s, C-'3, C-'4, C-6, C-7), 133.3, 132.3 (2s, C-4a, C-'1, C-8a), 121.5, 112.8, 111.4, 110.9, 110.6 (5d, C-8, C-'2, C-'6, C-'5, C-5), 56.1, 55.9 (2q, 4 x OCH_3), 51.46 (t, C-1), 39.7 (t, $\underline{CH}_2Ar$), 37.3 (t, C-3), 29.7 (d, C-4).

Mass data

m/z (%): 342 (M^+, 90), 339 (60), 229 (100).

(c) 6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline

(116, 0.1g, 20%)

mp. 126 - 127° lit.[74], m.p. 127 - 128°

All spectrum details agree with those quoted in previous experimental accounts.

2-Triphenylmethyl-4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (142)

2-Triphenylmethylisoquinolinium chloride (145, 2.0g, 0.004 mol) was stirred with saturated solution of sodium hydroxide (30 cm^3) for 3 hours, then the mixture was extracted with chloroform (2 x 25 cm^3). The combined organic layers were washed with water, dried over magnesium sulphate. Evaporation of the solvent gave colourless prisms (1.85g, 98%).

m.p. 156 - 158°

U.V.

λ_{max}(nm): 227, 277

I.R.

γ_{max}(cm^{-1}): 1610, 1595

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 7.55 - 7.4 (m, 5H, aromatics resonances of one

phenyl group), 7.3 - 7.05 (m, 10H, aromatics resonances of two phenyl groups), 6.75 - 6.6 (m, 3H, '2-H, '5-H. '6-H), 6.42 (s, 2H, 5-H, 8-H), 3.8 - 3.6 (3s, 12H, 4 x $O\underline{CH}_3$), 3.4 - 2.6 (complex, 7H, 4-H, 3-H, 1-H, $\underline{CH}_2Ar$) methine protons)

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 148.8, 147.4, 147.2, 147.0, (4s, C-6, C-7, C-'4, C-'3), 142.4 (s, $\underline{C}-(C_6H_5)_3$), 133.3, 130, 128.1 (3s, C-4a, C-8a, C-'1), 129.4 (d, $\underline{C}_6H_5$), 127.1 (d, 2 x $\underline{C}_6H_5$), 126.1, 121.2, 112.7, 111.5, 109.5 (5d, C-'2, C-'5, C-'6, C-8, C-3), 55.8, 55.7 (2q, 4 x $O\underline{CH}_3$), 52.1, 51.4 (2t, $\underline{CH}_2Ar$, C-1) 41.5, (t, C-3), 40.3 (d, C-4).

Mass data

m/z (%): FAB 585 (65), 467 (60), 335 (98).

C, 79.96; H, 6.71; N, 2.33; $C_{39}H_{39}NO_4$ requires:
C, 79.80; H, 6.72; N, 2.28%

Electrochemical oxidation of 2-triphenylmethyl-4-(3,4-dimethoxy benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (142)

The N-triphenylmethylisoquinoline (142, 0.5g, 0.0009 mol) in 0.1M sodium perchlorate in dry acetonitrile (300 cm^3) was electrolysed at an anode potential of 1.2 volts (vs SCE) and at current of 30mA for 1.5 hours. Then, the anolyte was separated, water (10 cm^3) was added and the mixture was evaporated to near dryness. The dark residue was dissolved in chloroform (55 cm^3),

washed with water (2 x 25 cm^3), the organic phase was dried over magnesium sulphate and evaporated to leave an oil which was chromatographed over silica using 30% ethyl acetate in dichloromethane as eluant to give the following products in order of the eluting from the column.

(a) Triphenylmethanol (144, 0.16g, 32%)
m.p. 159 - 160° lit.[77], m.p. 160°

(b) 6,7-Dimethyl-4-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroiso quinoline (122, 0.25g 50%).

Physical data for these products match those obtained previously.

Methyl-β-(3,4-dimethoxyanilino)propionate (148).

3,4-Dimethoxyaniline (147, 1.0g, 0.0065 mol) in dry benzene (25 cm^3), was heated with methyl acrylate (0.6g, 0.0065 mol) and glacial acetic acid (0.5 cm^3) under reflux conditions for 48 hours. Then, the solvent was evaporated to give a yellow oil. This was chromatographed over silica using 30% ethyl acetate in 60 - 80° petroleum ether as eluant to give the required ester as a colourless oil (1.25g, 80%).

U.V.

λ_{max}(nm): 242, 295

I.R.

γ_{max}(cm^{-1}): 3500 (NH), 1720 (C=O), 1610, 1595

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 6.8 (d, 1H, 6-H. J = 9Hz), 6.3 - 6.05 (m, 2H, 2-H, 5-H), 3.8, 3.75 (2s, 6H, 2 x OCH_3), 3.65 (s, 3H, OCH_3), 3.39 (t, 2H, N-CH_2, J = 5Hz), 2.50 (t,2H, $CH_2C^{\nearrow O}$, J = 5Hz).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 172.9 (s, C=O), 150.2, 142.8, 141.8 (3s, C-1, C-3, C-4), 113.7, 103.9, 99.6 (3d, C-2, C-5, C-6),56.8, 55.7 (2q, 2 x OCH_3), 51.6 (q, $C^{\nearrow O}-OCH_3$) 40.4, 33.9 (2t, CH_2-CH_2).

Mass data

m/z (%): 239 (M^+, 190), 224 (80), 213 (50), 166 (100).

Accurate mass measurement

Found: 239.1157 $C_{12}H_{17}NO_4$ requires:
239.1156

Methyl-N-tosyl-β-(3,4-dimethoxyanilino)propionate (149)

Methyl-β-(3,4-dimethoxyanilino)propionate (148, 1.0g, 0.0042 mol and p-toluene-sulphonyl chloride (0.8g, 0.004 mol) in dry benzene were stirred for 48 hours at room temperature. Evaporation of the solvent left colourless compound which was chromatographed by silica using 50% ethyl acetate in 60 - 80° petroleum ether to give needles compound (1.6g, 97%).

m.p. 95°

U.V.

λ_{max}(nm): 227, 285

I.R.

$\gamma_{max}(cm^{-1})$: 1730, 1600

^1H n.m.r.

δ(ppm, $CDCl_3$): 7.6 - 7.1 (m, 4H, aromatics), 6.8 - 6.4 (complex, 3H, aromatics), 3.8, 3.7 (2s, 9H, 3 x OCH_3), 3.81 (t, 2H, NCH_2-CH_2, J = 6Hz), 2.3 (t, $CH_2CH_2C(=O)$-, J = 6Hz), 2.4 (s, 3H, aryls CH_3).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 171.4 (s, C=O), 149.0, 143.6 (2s, C-4, C-3), 135.3 (s, C-1), 131.7 (s, C-CH_3), 130.2, 129.4, 127.9 (3d, C-'2, C-'3, C-'5, C-'6), 121.2, 112.8, 110.9 (3d, C-2, C-5, C-6), 55.9 (q, 2 x OCH_3), 51.6 (q, $C(=O)$-OCH_3), 47.2, 34.0 (2t, CH_2-CH_2), 21.5 (q, $ArCH_3$).

Mass data

m/z (%): 393 (M^+, 22), 238 (100).

Accurate mass measurement:

Found: 393.1243 $C_{19}H_{23}NO_6S$ requires: 393.1241

N-Tosyl-β-anilinopropionoic acid (150)

The previous ester (149, 2.1g, 0.0053 mol), 6N potassium hydroxide solution (1.1 cm^3) water (4.5 cm^3) and methanol (19 cm^3) were stirred for 3 days. Then, the mixture was acidified and extracted with chloroform (4 x 25 cm^3). The chloroform layer was washed with saturated sodium bicarbonate (2 x 20 cm^3) and the combined aqueous layers were acidified, re-extracted with chloroform

(2 x 25 cm^3) and the extracts dried over magnesium sulphate. Evaporation of the solvent left a colourless compound which was chromatographed over silica using 5% methanol in dichloromethane as eluant yield (1.7g, 88%).

m.p. 126°

I.R.

$\gamma_{max}(cm^{-1})$: 3400 - 3005 (broad), 1710, 1695

^1H n.m.r.

δ(ppm, $CDCl_3$): 8.6 (br.s, 1H, OH), 7.55 - 7.2 (q, 4H, aromatics), 6.8 - 6.5 (complex, 3H, aromatics), 3.83, 3.7 (2s, 6H, 2 x OCH_3), 3.80 (t, 2H, $-CH_2N$, J = 8Hz), 2.39 (t, 2H, $CH_2C(=O)-$, J = 8Hz), 2.4 (s, 3H, $Ar-CH_3$).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 176.5 (s, C=O), 149.0 (s, C-3, C-4), 143.6 (s, C-1), 135.0 (s, $-CSO_2$), 113.5 (s, $C-CH_3$), 129.4, 127.9 (2d, C-'4, C-'3, C-'5, C-'6), 121.1, 112.7, 110.95 (3d, C-2, C-5, C-6), 55.9 (q, 2 x OCH_3), 54.98, 46.8 (2t, CH_2CH_2), 33.8 (q, $Ar-CH_3$).

Mass data

m/z (100): 379 (M^+, 37), 224 (100).

Accurate mass measurement:

Found: 379.1087 $C_{18}H_{21}NO_6S$ requires 379.1086

N-Tosyl-3,4-dimethoxy-1,2,3,4-tetrahydroquinolin-4-one (151)

The acid from the previous experiment (150, 1.0g, 0.0052 mol) and phosphorus pentachloride (1.2g, 0.0058 mol) in dry benzene (10 cm^3) was stirred for 30 minutes at room temperature. Then the solvents were distilled off at 60 - 70° under reduced pressure. More benzene (15 cm^3) was added and the distillation continued. This process was repeated twice more and the residual acid chloride was eventually dissolved in dry benzene (15 cm^3) and added dropwise at 5° to a solution of aluminium chloride (1.0g, 0.0058 mol) in dry benzene, then, the mixture was stirred for 4 hours while the temperature was allowed to rise slowly to 22 - 24°. The mixture was chilled, ether (25 cm^3) was added and 1:1 cold hydrochloric acid solution was introduced with stirring at such a rate that the temperature remained below 15°. The organic layer was separated, washed with 1:1 hydrochloric acid solution (3 x 20 cm^3), then washed in succession with saturated sodium bicarbonate solution (20 cm^3), 5% potassium hydroxide (30 cm^3) and finally with water (2 x 20 cm^3). It was then dried over magnesium sulphate followed by chromatography over silica using 50% ethyl acetate in 60 - 80° petroleum ether to give the title compound as colourless needles (0.9g, 93%).

m.p. 92 - 93°

U.V.

λ_{max}(nm): 240, 330

I.R.

γ_{max}(cm^{-1}): 1670, 1600

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 7.6 - 7.15 (complex, 7H, 2 x aromatics)
4.20 (t, 2H, $\underline{CH_2}N$, $\underline{J}$ = 6Hz), 3.99, 3.90 (2s, 6H, 2 x $O\underline{CH_3}$),
2.35 (s, 3H, $\underline{CH_3}Ar$), 2.20 (t, 2H, $\underline{CH_2}C(=O)$, $\underline{J}$ = 6Hz).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 191.5 (s, C=O), 145.2 144.5 (2s, C-3, C-4),
137.7, 136.9 (2s, C-4a, C-1a), 130.0, 126.9 (2d, C-'2, C-'3,
C-'5, C-'6), 128.0 (s, SO_2-C), 119.3 (s, $\underline{C}$-CH_3), 108.0, 107.8
(2d C-2, C-5), 56.4, 56.6 (2q, 2 x $O\underline{CH_3}$), 46.8, 35.6 (2t, -$\underline{CH_2}$,$\underline{CH_2}$),
21.5 (q, $\underline{CH_3}$-Ar).

Mass data

m/z (%); 361 (M^+, 90), 206 (25), 195 (30).

Accurate mass measurement

Found: 361.4033 for $C_{18}H_{19}NO_5S$
requires: 361.4030

3,4-Dimethoxybenzyl bromide (94)

3,4-Dimethoxybenzyl alcohol (3.0g, 0.0018 mol) was dissolved in dry ether (50 cm^3) and to it was added freshly distilled phosphorus tribromide (4.86g, 0.0018 mol) at 0°, the mixture was allowed to stand overnight at room temperature, then washed with water (100 cm^3) and finally with saturated aqueous bicarbonate (100 cm^3); it was then dried over magnesium sulphate. Removal of the solvent under reduced pressure gave an oil which solidified on standing and which was crystallised as a colourless compound from ethanol (4.0g,97%).

m.p. , 28° lit.[78], m.p. 27 - 29°

U.V.

λ_{max}(nm): 278

I.R.

γ_{max}(cm^{-1}): 1600, 1595

^{1}H n.m.r.

δ(ppm, $CDCl_3$): 6.9 (s, 2H, 6-H, 5-H), 6.8 (s, 1H, 2-H), 4.45 (s, 2H, $C\underline{H}_2Br$), 3.85 (s, 6H, 2 x $OC\underline{H}_3$).

^{13}C n.m.r.

δ(ppm, $CDCl_3$): 149.1 (s, C-1), 138.4, 128.2 (2s, C-3, C-4), 121.6, 112.3, 111.2 (3d, C-5, C-6, C-2), 55.9 (q, 2 x $O\underline{C}H_3$), 34.3 (t, $\underline{C}H_2Br$).

Mass data

m/z (%): 231 (M^+, 76), 151 (100).

3,4-Dimethoxybenzyltriphenylphosphonium bromide (152)

Dry triphenylphosphine (3g, 0.012 mol) in dry benzene (35 cm^3) was added slowly to 3,4-dimethoxybenzyl bromide (94, 2.8g, 0.012 mol) in dry benzene (25 cm^3). The mixture was left stirring for 48 hours and the colourless precipitate which had formed was filtered off and washed with benzene to give the required salt (5.7g, 95%).

m.p. 247 - 248°

U .V.

λ_{max}(nm): 225

I.R.

γ_{max}(cm^{-1}): 1595, 1100, 1000.

The reaction between the ketone (151) and the Wittig reagent (152)

The Wittig reagent (152, 3.1g, 0.006 mol) was added to a solution of sodium (0.14g, 0.006 mol) in absolute ethanol (30 cm^3). The reaction mixture was stirred for 2 hours, then, the ketone (151, 2.16g, 0.006 mol) in dry ethanol (20 cm^3) was added dropwise at room temperature. The mixture was stirred for a further 24 hours, then the solvent was evaporated off to give an oily compound which was chromatographed over silica, using 30% ethyl acetate in 60 - 80° petroleum ether. Unfortunately, only starting material was returned.

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